Structured Equations for Complex Living Systems - Modeling, Asymptotics and Numerics

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Structured Equations for Complex Living Systems

Modeling, Asymptotics and Numerics

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To my parents, for their unconditionated love

Per aspera ad astra
Seneca, Hercules Furens

The scientific association with a big idea,
"the brand name", goes to the one who connects the dots
N.N. Taleb, The Black Swan: The Impact of the Highly Improbable

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Contents

Part I

Preface

More than three centuries ago, Isaac Newton became the revered founder of modern Mechanics due to his intuition, gathered by empirical evidence, about a possible mathematical formalization for the law of universal gravitation. A very simple equation, like the one by Newton, has allowed humankind to understand those principles that rule the motion of celestial bodies as well as to predict spectacular phenomena, such as solar eclipses, thousands of years in advance. From then on, the scientific community has been pervaded by the idea that many physical systems can be modeled in terms of a few fundamental principles so that, given the present state, their future behavior can be forecast by means of analytical calculations and numerical simulations.

However, we cannot deny the existence of several systems whose dynamics is less straightforward and, hence, scarcely foreseeable. We can predict a solar eclipse thousands of years in advance, but we are not able to predict the behavior of cancer cells in a few years or the poll results in a few months; we can say nearly nothing about the next day's Dow Jones index or about the behavior of a flock of birds in the next minutes. In one word, we are unable to precisely know in advance the evolution of systems composed of many interacting living agents.

What is the main difference between these systems and the ones whose evolution is well described by the laws of Classical Physics? They are *complex living systems* endowed with *self-organizing abilities* that result from the interactions among the constituent individuals of the system, which behave according to *specific functions, strategies or traits*. These functions/strategies/traits can evolve over time, as a result of *adaptation* to the surrounding environment, and are usually *heterogeneously* distributed over the individuals, so that the global features expressed by the system as a whole cannot be reduced to the superposition of the single functions/strategies/traits. Quoting Aristotle, we can say that, within these systems, "*the whole is more than the sum of its parts*" [3]. As a result, when we study the dynamics of complex living systems, there are new concepts that come into play, such as adaptation, herding and learning, which do not belong to the traditional vocabulary of physical sciences and make the dynamics of these systems hardly to be forecast.

During the last fifty years the study of complex living systems has become a major field of interdisciplinary research, which has considerably modified the international scientific landscape by leading to a deep interplay between researchers working in different areas. In particular, we have seen the arising awareness that Mathematics could play an active role in tackling some of the difficulties involved in studying these systems [6, 7]. In fact, consistent mathematical models can act as *virtual laboratories*, providing a framework where mechanisms that determine the behaviors of large groups of living beings can be understood more clearly. Moreover, mathematical models can be used to define some *hypothetical scenarios*, whose dynamics can be analyzed to reveal new insights into behaviors that have not yet been observed, thus reducing the gap between theory and experimental observation. In particular, as it has been pointed out in [6], while mathematical models of the inert matter have to reproduce qualitatively and quantitatively empirical data, mathematical models

of complex living systems should also reproduce, at least at a qualitative level, *emerging collective behaviors*, which cannot be directly related to the dynamics of a few individuals.

Modeling complex living systems requires, first of all, the definition of a strategy for reducing complexity in an empirically consistent way. The strategy here considered makes use of the mathematical formalisms for *structured and unstructured populations*. Unstructured models rely on the assumption that the individuals belonging to a given system can be treated as nearly identical and provide a mathematical description in terms of state variables like individual abundance, or density. As such, these models do not account for those functions/strategies/traits that can vary from one constituent to another, which can be useful to understand how mechanisms at the individual level generate phenomena at the global one. These features can be taken into account by introducing an independent variable, or a set of independent variables, standing for some characteristics that are heterogeneously distributed among the individuals composing the system. In other words, as pointed out in the the germinal works by Sharpe and Lotka in 1911 [62] and McKendrick in 1926 [51], unstructured models can be structured by additional variables, the so-called *structuring parameters*, or structuring variables, here assumed to belong to a given subset of $\mathbb{R}^d$, with $d \geq 1$, in order to define structured models.

Moving from the considerations drawn above, this work is conceived as a *collection of personal contributions* to the mathematical modeling of complex living systems, that is, models that we have presented in published/accepted/submitted journal papers and book chapters. These models are aimed at showing how the mathematical formalism under consideration allows to *qualitatively reproduce* phenomena arising in the realm of complex living systems.

Three main parts follow an introduction meant to define a common conceptual and mathematical background. These parts are divided into different chapters, each one referring to a specific model and providing *a brief summary* of the related aims, underlying assumptions and analytical/computational results. For a detailed presentation of the models, we refer the reader to the last part of this work, i.e. an appendix collecting the original papers. Let us point out that, in order to make this work self consistent, at least to a certain extent, with respect to the original papers, the contents here presented rely on notations stated by the introductory part, while original, and actually heterogeneous, notations have been maintained throughout the appendix.

In more detail:

Part II gives an *overview on the critical aspects involved in the mathematical modeling of complex living systems*. In particular:

> **Chapter 1** highlights some properties that make living systems to be complex, summarizes the possible representation scales for complex living systems and describes the strategy used in this work to reduce complexity in view of the mathematical modeling.

Chapter 2 presents some models for continuous structured populations so far developed to describe the dynamics of complex living systems, both in the biological and in the socio-economic context. The focus is on those structures that are actually used in this work only, i.e. phenotype-structured equations, space-velocity-structured equations (i.e. kinetic-like equations) and opinion-structured equations. A concise description of the main underlying hypothesis, related analytical aspects and numerical methods to perform simulations is provided.

Part III deals with phenotype-structured equations for the dynamics of *living species*. In particular:

Chapter 3 presents a class of integro-differential equations arising in evolutionary biology to model the dynamics of specialist and generalist species related by facultative mutualistic interactions. These equations are able to reproduce Darwinian evolution and speciation.

Chapter 4 is about phenotype structured equations modeling the dynamics of species related by predation. The effects of mutations, proliferation through asexual reproduction and competition for resources are included in the model, which can mimic the formation of evolutionary branching patterns.

Chapter 5 introduces a multi-dimensional integro-differential equation for the dynamics of habitat-specialist and habitat-generalist species endangered by habitat shrinking and global warming. This equation can be used to describe the evolution of endangered species under different hypothetical scenarios.

Part IV presents some models for the dynamics of *multicellular systems*. Apart from the ones introduced in Chapter 6 and Chapter 12, all these models rely on a hybrid structured-unstructured population formalism. The focus is on tumor cell dynamics, cancer-therapies, cancer-immune competition and immune system diseases. In more detail:

Chapter 6 deals with an unstructured population model for the cell dynamics inside colorectal crypts, which describes cancer progression as well as the generation, through successive mutations, of multiple subpopulations of cells at different progression stages.

Chapter 7 introduces a mathematical model for the dynamics of malignant hepatocytes under the effects of cytotoxic and targeted therapeutic agents. This model is aimed at enlightening the causes for emerging phenomena commonly observed in cancer progression, in general, and hepatocellular carcinoma, in particular.

Chapter 8 presents a model for the dynamics of cancer hepatocytes expressing epithelial and mesenchymal phenotypes, which move via chemotaxis, proliferate and interact among themselves. The model is aimed at mimicking, at least qualitatively, some collective behaviors experimentally observed in cancer hepatocyte monolayers.

Chapter 9 deals with the derivation, by formal asymptotic methods, of macroscopic equations for a space-velocity-structured equations describing the dynamics of epithelial and mesenchymal cells. The resulting macroscopic equations are able to reproduce biologically consistent scenarios.

Chapter 10 presents a model for immune response against cancer, which reproduces evolutionary scenarios related to the iterative selection exerted by the immune system over cancer cells, including recognition, learning and memory aspects of the immune response.

Chapter 11 describes a model that mimics the action of the immune system against self and non-self antigens as well as the initiation of autoreactivity, with particular reference to the roles played by T-cells.

Chapter 12 introduces a phenotype-structured model motivated by the theory of mutation-selection in adaptive evolution, which describes the dynamics of healthy and tumor cells under the effects of cytotoxic and cytostatic drugs. This model is meant to support the design of optimized anti-cancer strategies.

It is worth noting that most of these models stem from *direct collaborations with biologists and clinicians*. In particular, those presented in Chapter 7, Chapter 8 and Chapter 9 take advantage of fruitful discussions with W. Mikulits and his co-workers (Institute of Cancer Research, University of Vienna, Vienna, Austria); the models described in Chapter 10 and Chapter 11 rely on a direct collaboration with U. Dianzani and M. Melensi (Interdisciplinary Research Center of Autoimmune Diseases, Università del Piemonte Orientale, Novara, Italy); finally, the model discussed in Chapter 12 has been defined in cooperation with M.E. Hochberg (Institut des Sciences de l'Evolution, CNRS, Université Montpellier 2, Montpelier, France).

Part V focuses on continuous structured population models for opinion formation within *socio-economic systems*. In more detail:

Chapter 13 deals with the asymptotic behavior of mathematical models for opinion dynamics under bounded confidence of Deffuant-Weisbuch type. In particular, a theorem establishing the weak convergence of the solution to a sum of Dirac masses and characterizing the concentration points for different values of the model parameters is provided.

Chapter 14 presents a hybrid model for opinion formation in a large group of agents exposed to the persuasive action of a small number of strong opinion leaders. The model is defined by coupling a finite difference equation for the dynamics of leaders opinion with a continuous integro-differential equation for the dynamics of the others. The asymptotic behavior in time of the related solution is characterized under distinct scenarios, where different emerging behaviors can be observed.

Chapter 15 introduces a class of integro-differential equations modeling the dynamics of a market where agents estimate the value of a given traded good. Two basic mechanisms are assumed to concur in value estimation: interactions between agents and some sources of public information and herding phenomena. The asymptotic behavior in time of the related solution is characterized for some general parameter settings, which mimic different economic scenarios.

Part VI is devoted to draw conclusions and provide hints on *future researches*.

Appendix collects the published/accepted/submitted papers and book chapters where the models summarized by Part III, Part IV and Part V have been originally presented.

Part II

Conceptual and Mathematical Foundations

Introduction

All considered what is termed
wisdom to be conversant about
first causes and principles
Aristotle, Metaphysics

This part gives an overview on the critical aspects involved in the mathematical modeling of complex living systems. In particular:

- Chapter 1 highlights some properties that make living systems to be complex, summarizes the possible representation scales for complex living systems and describes the strategy used in this work to reduce complexity in view of the mathematical modeling.

- Chapter 2 presents some models for continuous structured populations so far developed to describe the dynamics of complex living systems, both in the biological and in the socio-economic context. The focus is on those structures that are actually used in this work only, i.e. phenotype-structured equations, space-velocity-structured equations (i.e. kinetic-like equations) and opinion-structured equations. A concise description of the main underlying hypothesis, related analytical aspects and numerical methods to perform simulations is provided.

Chapter 1

Preliminary aspects

This chapter presents preliminary aspects useful for the mathematical modeling of complex living systems. In more detail:

Section 1.1 aims at highlighting some of those properties that make living systems complex and impact on the development of mathematical models.

Section 1.2 deals with a concise introduction to the possible representation scales for complex living systems, from the microscopic to the macroscopic through the mesoscopic one.

Section 1.3 describes the strategy used in this work to reduce complexity in view of the mathematical modeling.

1.1 Complexity in living systems

Distinguishing features that make a system belonging to the realm of inert matter complex were already identified in the past [63]. *In nomine omen*, complex systems are classically defined as made up of a large number of parts that interact in a nonlinearly additive way. On the other hand, defining complexity in living systems is a more challenging task. This is basically due to the wide spectrum of behaviors expressed by living beings, which implies a lack of the invariants characterizing the constituents of inanimate systems. Hence, those properties that embody complexity in living systems need to be defined at a general and qualitative level, so that they can be tailored for fitting to specific cases.

A brief qualitative analysis of complex living systems is here developed, which takes advantage of several inspirational ideas proposed in [6, 7]. This analysis acts as a preparatory step toward the mathematical modeling. As such, it does not claim to be exhaustive and includes only those aspects that are effectively retained by the models presented in this work:

1. Large number of components.
Complex living systems are composed of *many interacting entities*. Therefore, because of the many degrees of freedom, a huge amount of variables is required, in principle, to describe the overall state of such systems in mathematical terms.

2. Peculiar functions/strategies/traits.
Despite the constituents of inert matter, the individuals composing living systems express some peculiar *functions/strategies/traits*. For instance, several species of birds have bright-colored feathers for reproductive purposes; human behaviors reflect personal opinions; firms follow precise marketing/pricing strategies to achieve revenue optimization; cells are characterized by different phenotypes and antigenic expressions. As a result, the mathematical modeling of living systems implies a reinterpretation of those axioms and structures that have been developed to describe the dynamics of inert matter.

3. Heterogeneity.
These *functions/strategies/traits* are *heterogeneously distributed* over the individuals belonging to the system. Namely, several gradations in color can be found in the birds' feathers; a plethora of different opinions with respect to the same statement may be expressed by human beings; revenue optimization strategies can strongly vary from one firm to another; cells holding the same genotype may express several different phenotypes. Such heterogeneity is one of the reasons why modeling the dynamics of living systems can be extremely difficult.

4. Time evolving functions/strategies/traits and self-organized behaviors.
Individuals belonging to living systems are lead to *modify their functions /strategies/traits over time*, in order to adapt to the evolution of the context defined by the *inner environment* (i.e. the other individuals inside the system) and the *outer environment* (i.e. exogenous actions). For example, focusing on socio-economic systems, we can merely note that people can change their opinions over time, both in a spontaneous way and due to the pressures exerted by their social context or by the mass media. On the other hand, making reference to biological systems, an illuminating example of this fact is provided by Darwinian adaptation:

> "I can see no limit to the amount of change, to the beauty and complexity of the co-adaptations between all organic beings, one with another and with their physical conditions of life, which may have been effected in the long course of time through Nature's power of selection, that is by the survival of the fittest" [23].

The evolution of individual functions/strategies/traits results into *collective phenomena* highlighted by *self-organized behaviors* [16, 20, 21, 27, 29], such as *herding*, *adaptation* and *learning*. Herding phenomena occur when individuals observe and replicate the behavior of other individuals, while learning phenom-

ena and adaptation take place when a subject is lead to modify a personal strategy or a given trait as a result of the pressure exerted by the inner and/or the outer environment.

5. Nonlinear interactions and emergent phenomena.
The overall behavior of complex living systems is determined by the interactions occurring among their constituents. However, a traditional mathematical modeling of individual dynamics does not lead to a straightforward description of collective behaviors. In fact, individuals interact with each other in a *nonlinearly additive* way and the superposition principle is lost. As a consequence, the dynamics of the system as a whole is more than the superposition of the individual dynamics of its single constituents, i.e. "the whole is more than the sum of its parts" [3]. This paves the way to the occurrence of self-organization and *emergent phenomena* [19, 22].

6. Function/strategy/trait dependent interactions.
The laws ruling *interactions in living systems*, if it is possible to identify any law, are strongly *affected by the peculiar functions/strategies/traits* expressed by the interacting individuals. For instance, competition is stronger between animal species that consume the same resources; people whose opinions are too far apart do not trust each other, so they are used to avoid mutual interactions; some immune cells are only able to recognize malignant cells expressing certain antigens; in many cases of practical interest for socio-economic sciences, "interactions between individuals are channeled through specialized communication-transportation networks" [65], which organize and select the interacting subjects. Therefore, those laws that have been introduced to model interactions among constituents of the inert matter do not suffice for describing the dynamics of living beings in mathematical terms.

1.2 A matter of representation scales

Mathematical modeling requires a transition from real systems to the abstract language of Mathematics; this implies a careful introductory analysis of the system under consideration. Such analysis aims at identifying the phenomena to be modeled, as well as a suitable representation scale, and it is a crucial step toward a worthwhile description in terms of a reasonable number of key variables.

The proper scale can be chosen among the ones traditionally used for modeling inert matter, i.e. *microscopic scale*, *macroscopic scale* and *mesoscopic scale*. Representation at each scale relies on different mathematical structures, which are grounded on technical approximations and suffer from either analytical or computational drawbacks.

At the microscopic scale, each single constituent of the system is viewed as a whole. Its physical state is characterized by means of some dependent variables, whose evolution is generally ruled by a set of *ordinary differential equations*. On

the contrary, the macroscopic scale refers to observable quantities which can be mathematically recovered as local averages over the microscopic states, at least in those cases where the system is composed of a sufficiently large number of elements. Models at this scale are generally stated in terms of *partial differential equations*, where macroscopic observables play the role of dependent variables.

Due to the very large number of components in the game within complex living systems, dealing with single individuals, as at the microscopic scale, can be mathematically unwieldy. On the other hand, the process leading to a macroscopic description is an averaging process and, as such, it hides the peculiar properties expressed by the individuals belonging to living systems. Such limitations can be overcome by the representation pertaining to the mesoscopic scale. In fact, at this scale, the state of the whole system is characterized by a suitable function, or a set of functions, describing the distribution of individuals over the microscopic states, and macroscopic quantities are naturally recovered as successive moments of these functions. Models at the mesoscopic scale are stated in terms of *partial differential equations*, where even *integral terms* can be included, which describe the evolution of this function, or these functions, on the basis of microscopic interactions.

Although the constituents of microscopic and macroscopic scales are well established in the case of inert matter, this distinction is usually more vague in the case of living systems. In general, the microscopic representation can be related to an atomistic description in terms of single interacting agents (e.g. cells, people, financial market and firms), while the macroscopic representation can be referred to a systemic description involving those structures/processes that result from the interactions among microscopic agents (e.g. organs, collective opinions, market indexes and market trends). The mesoscopic scale is a sort of *intermediate scale*; in fact, the related representation allows to bring to light the existing connections between the microscopic interactions and the macroscopic features of the system viewed as a whole.

1.3 A joint structured-unstructured population approach to handle complexity

The development of mathematical models for complex living systems calls for the definition of a strategy to *reduce complexity* in an empirically consistent way. Our strategy makes use of the mathematical formalisms for *structured and unstructured populations* (see for instance [42, 60] and references therein) and takes advantage, from a conceptual perspective, of the idea presented in [6, 7].

At this stage, let us recall that *unstructured models* rely on the assumption that the individuals of a given system, in particular a given population, can be treated as nearly identical and provide a mathematical description in terms of state variables like individual abundance, or density. As such, these models do not account for those functions/strategies/traits that can vary from one individual to another, which can be useful to understand how mechanisms at

the individual level generate phenomena at the population one. For this reason an independent variable, or a set of independent variables, can be introduced, standing for some functions/strategies/traits of interest that are heterogeneously distributed among the individuals of the population, or more in general the system, under consideration. In other words, as it has been noted in the germinal works by Sharpe and Lotka in 1911 [62] and McKendrick in 1926 [51], unstructured models can be structured by additional variables, the so-called *structuring parameters or structuring variables*, in order to define *structured models*. Such variables are usually assumed to belong to a given subset of $\mathbb{R}^{d\geq 1}$ and they can be related both to certain characteristics that evolve over time and/or to some other features whose rate of change with respect to time can be assumed equal to zero, at least for modeling purposes.

Our strategy to reduce complexity consists of the following five steps:

Step 1. Selection of the representation scale.
As previously noted, the first step toward the mathematical modeling of real-world systems consists in defining a proper representation scale. On the basis of the considerations drawn in Section 1.2, we focus on the *mesoscopic scale*, where the state of the whole system is characterized by a suitable set of functions describing the distribution of the interacting individuals over the microscopic states. Macroscopic quantities are recovered through integration.

Step 2. Partition of the system into subpopulations.
Living systems are usually composed of a large variety of interacting components. In some cases, this variety can be so large that the analytical and numerical tools developed for modeling cannot be effectively applied. However, this difficulty can be tackled by grouping the interacting components into some *subpopulations*, according to empirically consistent principles, and studying both the interactions *among* subpopulations and the interactions *within* each subpopulation. In one word: *divide et impera*.

For instance, in cancer modeling, distinct subpopulations can be defined as normal cells, cancer cells and immune cells that are able to recognize cancer cells. On the other hand, focusing on models for living species, subpopulations can be defined by groups of animals belonging to the same species and consuming the same resources. Finally, with reference to models for socio-economic systems, a subpopulation can be defined by investors in the same market or by people belonging to the same social group. It is worth noting that this approach applies both if the components of the system are *individual subjects*, such as single cells, animals or people, or *collective subjects*, such as whole organs, species, market or social groups.

Subpopulations and functions/strategies/traits should be properly identified according to the objectives of the investigations and the purposes of the analysis to be developed. The functions/strategies/traits of interest can be heterogeneously distributed among the components, that is, each individual expresses the same function/strategy/trait of the other ones but in a different way. With reference to the aforementioned examples, cancer cells can express differ-

ent levels of malignancy, animal belonging to a given specie can consume the same resources at different rates, investors in the same market can hold different portfolios and people belonging to the same social group can have distinct opinions about the same topic. However, according to the modeling purposes, in order to provide a consistent description of the complex system under consideration, there are some subpopulations where this heterogeneity needs to be taken into account and some others where the identifying function/strategy/trait can be seen as homogeneously distributed over the subpopulations, that is, individuals can be seen as identical to each other (i.e. on average, they express the functions/strategies/traits of interest in the same way).

Different modeling strategies, and so different mathematical structures, should be introduced to describe the dynamics of subpopulations, according to the fact that the heterogenous expression of the functions/strategies/traits of interest is, or it is not, relevant to the system to be modeled. As a result, we divide subpopulations into two wide classes: *structured subpopulations* and *unstructured subpopulations*. From now on, we focus on a set of I structured subpopulations and J unstructured subpopulations, labeled by index $i = (1, ..., I)$ and $j = (1, ..., J)$, respectively.

Step 3. Assessment of the microscopic state.
For each i^{th} subpopulation, a suitable set of variable has to be selected to model the functions/strategies/traits of interest, which identify the *microscopic state* of the individuals and act as *structuring variables* for the subpopulation. Here we refer to such variables as $\mathbf{s} \in S \subseteq \mathbb{R}^{d \geq 1}$, which can be dimensionless or expressed in units of some suitable reference quantities depending on the system to be modeled.

Step 4. Characterizing the state of each subpopulation.
Suitable mathematical structures are required to model the state of both structured and unstructured subpopulations, and so the state of the whole system. Let us assume that the system is observed on a time interval $[0, +\infty)$, or eventually $[0, T]$, and introduce the following set of functions:

$$\begin{cases} f_i = f_i(t, \mathbf{s}) : \mathbb{R}^+ \times S \to \mathbb{R}^+ & \text{for} \quad i = 1, ..., I \\ n_j = n_j(t) : \mathbb{R}^+ \to \mathbb{R}^+ & \text{for} \quad j = 1, ..., J. \end{cases} \tag{1.1}$$

For any fixed time t, $n_j(t)$ stands for the number of individuals in subpopulation j normalized with respect to the total number of individuals inside the system at time $t = 0$. On the other hand, the quantity $f_i(t, \mathbf{s})\, d\mathbf{s}$ stands for the number of individuals in subpopulation i whose microscopic state belongs to the volume element $d\mathbf{s}$ centered at $\mathbf{s}$, again normalized with respect to the total number of individuals inside the system at time $t = 0$. The state of subpopulations i and j are described by functions f_i and n_j, respectively. The *size of subpopulation* i and the *total size of the whole system* are computed, respectively, as

$$\varrho_i(t) = \int_S f_i(t, \mathbf{s}) d\mathbf{s}, \quad \varrho(t) = \sum_{j=1}^{J} n_j(t) + \sum_{i=1}^{I} \varrho_i(t); \tag{1.2}$$

thus, empirical consistency implies

$$f_i(t,\cdot) \in L^1(S), \qquad \forall\, t \geq 0,$$

or, at least, that $f_i(t,\cdot) \in L^1_{loc}(S)$ for all $t \geq 0$.

Step 5. Definition of suitable evolution equations.
The dynamics of each function $n_j(t)$ is governed by a model describing the net inlet and outlet of individuals through the j^{th} subpopulation at time t. These models are stated in terms of ordinary differential equations and can be referred to the following class of differential systems:

$$d_t n_j(t) = \mathcal{N}_j[\mathbf{n}](t), \quad t \in \mathbb{R}^+, \tag{1.3}$$

where $\mathbf{n} = \{n_j\}_{j=1}^J$, while functional $\mathcal{N}_j$ describes the net flux of individuals through subpopulation j at time t and it can be generally defined as follows:

$$\mathcal{N}_j[\mathbf{n}](t) := \mathcal{P}_j[\mathbf{n}](t) n_j(t) + \mathcal{M}_j[\mathbf{n}](t), \tag{1.4}$$

where functional $\mathcal{P}_j$ models the net proliferation rate at time t while functional $\mathcal{M}_j$ stands for the net inflow of individuals in subpopulation j due to the fact that individuals can modify their subpopulation over time, also due to interactions among themselves.

In a similar way, the evolution of functions $f_i(t,\mathbf{s})$ is described by a suitable set of partial differential, or integro-differential, equations modeling the net inlet of individuals in the elementary volume $d\mathbf{s}$ centered in $\mathbf{s}$ of subpopulation i:

$$d_t f_i(t,\mathbf{s}) = \partial_t f_i(t,\mathbf{s}) + \nabla_{\mathbf{s}} \cdot (\Gamma(\mathbf{s}) f_i(t,\mathbf{s})) = \mathcal{F}_i[\mathbf{f}](t,\mathbf{s}), \quad t \in \mathbb{R}^+, \quad \mathbf{s} \in S. \tag{1.5}$$

In the above equations, $\mathbf{f} = \{f_i\}_{i=1}^I$, functional Γ is the evolution rate over time (i.e. the evolution speed) of $\mathbf{s}$, while functional $\mathcal{F}_i$ describes the net flux of individuals of subpopulation i through the volume element $d\mathbf{s}$ centered in $\mathbf{s}$ at time t, due to the phenomena and the interactions under consideration. The definitions of $\Gamma(\mathbf{s})$ and $\mathcal{F}_i[\mathbf{f}](t,\mathbf{s})$ depend on the system to be modeled and can vary according to the empirical meaning of $\mathbf{s}$. Some possible definitions are provided by the following chapter, which rely on the mathematical formalism for continuous structured populations.

The evolution of functions (1.1) can be described through suitable combinations of Eqs. (1.3) and Eqs. (1.5) as the one given hereafter,

$$d_t \mathbf{h}(t,s) = \mathcal{H}[\mathbf{h}](t,\mathbf{s}), \quad t \in \mathbb{R}^+, \quad \mathbf{s} \in S, \tag{1.6}$$

where

$$\mathbf{h}(t,\mathbf{s}) = \left(f_1(t,\mathbf{s}), ..., f_I(t,\mathbf{s}), n_{I+1}(t), ..., n_{I+J}(t)\right),$$

and $\mathcal{H}[\mathbf{h}](t,\mathbf{s})$ is componentwise defined by functionals $\{\mathcal{F}_i\}_{i=1}^I$ and $\{\mathcal{N}_j\}_{j=1}^J$, eventually with suitable modifications allowing to include interactions between structured and unstructured subpopulations.

Before ending this chapter, let us briefly remark that the joint structured-unstructured population approach here considered makes it possible to effectively model the complexity aspects of living systems summarized in Section 1.2. In fact, dividing the reference system into several interacting subpopulations, it is possible to deal with complex systems composed of many interacting individuals. Furthermore, the mesoscopic description and those structures that pertain to the mathematical formalism for populations structured by continuous variables allow to take into account the heterogeneous functions/strategies/traits expressed by living beings as well as to model those nonlinear interactions that make these functions/strategies/traits evolve over time, leading to the emergence of self-organized behaviors. These aspects will become more evident at the end of this work, after the presentation of the results that we have so far obtained through such a modeling approach.

Chapter 2

Models and methods for structured populations

The present chapter provides a brief overview on the mathematical structures here used to model the dynamics of structured subpopulations. In particular, we illustrate some of the models for continuous structured populations so far developed to describe the dynamics of complex living systems, both in the biological and in the socio-economic context. Since the focus is on structures that are actually used in this work, age- and size-structured equations are not considered and the contents of the chapter are organized as follows:

Section 2.1 deals with populations structured in phenotypes.

Section 2.2 focuses on populations structured in space position and velocity.

Section 2.3 refers to populations structured by the opinions of individuals.

Each section summarizes the underlying hypothesis and mathematical structures of the models as well as some of the related analytical aspects and numerical methods to perform simulations.

2.1 Populations structured in phenotypes

In the biological context, there are many situations where populations can be structured making use of traits that are inherited by the individuals from their parents and that refer to the value for adults, the so-called phenotypic traits (e.g. the ability of individuals to ingest specific resources). In these cases, the $\mathbf{s}$ variables can be assumed to not vary over time and the identity below holds true:

$$\Gamma(\mathbf{s}) = 0, \quad \forall\, \mathbf{s} \in S,$$

where function Γ refers to Eq. (1.5). Furthermore, if sexual interactions can be neglected and mutations from parents to offspring introduce only small changes in the phenotypic traits, functional $\mathcal{F}_i$ in Eq. (1.5) can be defined in the following general way

$$\mathcal{F}_i[\mathbf{f}](t,\mathbf{s}) := \mathcal{P}_i[\mathbf{f}](t,\mathbf{s})f_i(t,s) + \mathcal{M}_{\varepsilon i}[\mathbf{f}](t,\mathbf{s}), \tag{2.1}$$

where functional $\mathcal{P}_i$ denotes the net per capita growth rate of population i, while functional $\mathcal{M}_{\varepsilon i}$ describes the effects of mutations leading individuals belonging to a certain population and expressing certain traits to give birth to offspring that can be associated to a different population and/or that express different traits. The average size of variations in the phenotypic traits is modeled by the small parameter ε. Such functionals can be defined in different ways according to the modeling purposes.

2.1.1 Mathematical models

For instance, focusing on the dynamics of one single population, i.e. $I = 1$ and $\mathbf{f}(t,\mathbf{s}) = f(t,\mathbf{s})$, we can take advantage of the considerations drawn in [47, 53, 60] and introduce the following alternative definitions:

$$\mathcal{P}[f](t,\mathbf{s}) := \kappa(\mathbf{s}) - \int_S \mu(\mathbf{s}_*,\mathbf{s})f(t,\mathbf{s}_*)d\mathbf{s}_* \tag{2.2}$$

and

$$\mathcal{M}_\varepsilon[f](t,\mathbf{s}) := \int_S \theta(\mathbf{s}_*)M(\mathbf{s},\mathbf{s}_*;\varepsilon)f(t,\mathbf{s}_*)d\mathbf{s}_* - \theta(\mathbf{s}), \tag{2.3}$$

or

$$\mathcal{P}(t,\mathbf{s}) := \frac{r(\mathbf{s})}{(1+\varrho(t))^\beta} - d(\mathbf{s}) \tag{2.4}$$

and

$$\mathcal{M}_\varepsilon[f](t,\mathbf{s}) := \int_S \frac{\theta(\mathbf{s}_*)r(\mathbf{s}_*)}{(1+\varrho(t))^\beta}M(\mathbf{s},\mathbf{s}_*;\varepsilon)f(t,\mathbf{s}_*)d\mathbf{s}_* - \theta(\mathbf{s})\frac{r(\mathbf{s})}{(1+\varrho(t))^\beta}. \tag{2.5}$$

In the above equations:

- Function $\theta(\mathbf{s}_*)$ is the mutation rate of individuals expressing traits $\mathbf{s}_*$, while kernel $M(\mathbf{s},\mathbf{s}_*;\varepsilon)$ denotes the probability that mutations make a parent individual with phenotypic traits $\mathbf{s}_*$ give birth to offspring with traits $\mathbf{s}$. As a probability kernel, M satisfies the following identity

  $$\int_S M(\mathbf{s},\mathbf{s}_*;\varepsilon)d\mathbf{s} = 1, \qquad \forall\ \mathbf{s}_* \in S \text{ and } \forall\ \varepsilon > 0.$$

  Since mutations introduce only small phenotypic changes from parents to offspring, M can be considered negligibly small for $\mathbf{s}$ outside an ε-neighborhood of $\mathbf{s}_*$ and

  $$M(\mathbf{s},\mathbf{s}_*;\varepsilon) = M\left(\mathbf{s}-\mathbf{s}_*;\varepsilon\right).$$

- Function $\kappa(\mathbf{s})$ stands for the proliferation rate of individuals expressing traits $\mathbf{s}$, while function $\mu(\mathbf{s}_*, \mathbf{s})$ represents the death rate of individuals with phenotypic traits $\mathbf{s}$ due to the competition, namely for space and resources, with other individuals expressing traits $\mathbf{s}_*$.

- Function $r(\mathbf{s})$ is the proliferation rate of individuals assumed to be limited by factor $\frac{1}{(1+\varrho(t))^\beta}$, which depends on the size of the population. Parameter β measures, on average, how strongly the chance for the birth of new individuals is influenced by the total size of the population. Function $d(\mathbf{s})$ models the death rate of individuals expressing traits $\mathbf{s}$ due to natural causes.

Definitions (2.2) and (2.3) rely on the idea that population growth is hampered by competitive interactions, while definitions (2.4) and (2.5) take into account other saturation effects not mediated by interactions, such as reducing over time those resources that are required by individuals to proliferate, which comes along with population growth. Both modeling strategies mimic the same effects of net proliferation/death and prevent the case $\varrho(t) \to \infty$, that would correspond to a not empirically consistent blow up in the number of individuals.

Definitions (2.2) and (2.4) can also be coupled to the following alternative definition of functional $\mathcal{M}_\varepsilon$

$$\mathcal{M}_\varepsilon[f](t, \mathbf{s}) := \varepsilon^2 \Delta f(t, \mathbf{s}), \tag{2.6}$$

where the effects of mutations are modeled through the Laplace term, while parameter ε^2 stands for the average mutation rate.

2.1.2 Asymptotics

If the time scales of selection and mutation are assumed to be separated, i.e. mutations are rare with respect to birth and death processes, parameter ε can be used to model also the ratio between these two time scales. Then, if time is rescaled setting

$$f_\varepsilon(t, \mathbf{s}) = f\left(\frac{t}{\varepsilon}, \mathbf{s}\right), \tag{2.7}$$

in those cases where $\mathcal{P}$ does not depend explicitly on f, Eq.(1.5) can be rewritten as follows:

$$\varepsilon \partial_t f_\varepsilon(t, \mathbf{s}) = \mathcal{P}(t, \mathbf{s}) f_\varepsilon(t) + \mathcal{M}_\varepsilon[f_\varepsilon](t, \mathbf{s}). \tag{2.8}$$

Time rescaling (2.7) has been proposed in [26] to consider the dynamics of populations on a time scale longer than the one of a single generation and asymptotic analysis can be developed in the limit $\varepsilon \to 0$ (i.e. in the limit of large times and small/rare mutations), with the aim of proving the convergence (in a suitable weak sense) of f_ε to a population density $\hat{f}$ that concentrate as a sum of Dirac masses, that is

$$\hat{f}(t, \mathbf{s}) := \sum_{n=1}^{N} \varrho_n(t) \delta(\mathbf{s} - \hat{\mathbf{s}}_n(t)), \quad \sum_{n=1}^{N} \varrho_n(t) = \varrho(t),$$

where $\delta(\cdot)$ is the Dirac's delta distribution and the set $\{\hat{\mathbf{s}}_n(t)\}_{n=1}^N$ defines the support of $\hat{f}(t,\mathbf{s})$ at time t.

From an ecological perspective, this kind of convergence results provide a possible mathematical formalization for the selection principle of evolutionary biology: a population initially dispersed over several traits, concentrates, for large time, along few of them, which can be interpreted as the fittest ones. Even more, if f_ε is concentrated in one single point $\mathbf{s}_0$ at time $t = 0$ (i.e. the population is monomorphic at the beginning of observations) and the assumptions over functionals $\mathcal{P}$ and $\mathcal{M}$ allow the convergence to a sum of Dirac masses $\hat{f}$ (i.e. the population becomes polymorphic across time), then also branching processes can be caught by this formalism.

Such concentration phenomena have been studied in [25] for one population structured by a single phenotypic trait (i.e. S is defined as a compact subset of $\mathbb{R}$) without mutations. On the other hand, both mutation and competition phenomena have been considered in [5, 26, 48, 61] again for one population but structured by multiple phenotypic traits (i.e. S is identified with the whole space $\mathbb{R}^d$). The hypothesis introduced in [25] allow $\hat{f}$ to be a sum of Dirac masses (i.e. branching processes can be reproduced), while only one single Dirac mass can be sustained under the assumptions considered in [5, 26, 48, 61] (i.e. only the dynamics of monomorphic populations can be modeled).

2.1.3 Numerics

Cauchy Problems linked to phenotype-structured equations can be solved introducing a suitable discretization $\{\mathbf{s}_k\}_k$ of the S domain and making use of implicit-explicit finite difference schemes, such as the one given hereafter, which refers to a one single population case where $\mathcal{P}$ does not depend explicitly on f:

$$\begin{aligned}\frac{f(t+dt,\mathbf{s}_k)-f(t,\mathbf{s}_k)}{dt} &= [\mathcal{P}_+(t,\mathbf{s}_k)-\mathcal{P}_-(t+dt,\mathbf{s}_k)]\,f(t,\mathbf{s}_k)\\ &+ \mathcal{M}_\varepsilon[f](t,\mathbf{s}_k).\end{aligned}$$

Functions $\mathcal{P}_+$ and $\mathcal{P}_-$ stand, respectively, for the positive and negative part of the $\mathcal{P}$ function. In this way, the original integro-differential initial value problem is approximated by a set of ordinary differential initial value problems, one for each equation describing the evolution of $\{f(t,\mathbf{s}_k)\}_k$, which can be solved using standard methods for ODEs (see, for instance, [45]).

2.2 Populations structured in space and velocity

When the focus is on the motion of individuals, populations can be structured by space and velocity variables, namely $\mathbf{s} := (\mathbf{x},\mathbf{v})$, so that S coincides with the phase space $X \times V \subseteq \mathbb{R}^{d_x} \times \mathbb{R}^{d_v}$, with $1 \le d_x, d_v \le 3$. In absence of external forces acting on the individuals' motion, the following identities hold true

$$\Gamma(\mathbf{x}) = \mathbf{v}, \qquad \Gamma(\mathbf{v}) = 0, \qquad \forall\,(\mathbf{x},\mathbf{v}) \in X \times V$$

and Eq.(1.5) can rewritten as follows:

$$\partial_t f_i(t,\mathbf{x},\mathbf{v}) + \mathbf{v}\cdot\nabla_{\mathbf{x}} f_i(t,\mathbf{x},\mathbf{v}) = \mathcal{F}_i[\mathbf{f}](t,\mathbf{x},\mathbf{v}), \tag{2.9}$$

where the gradient term models the transport of individuals with their own velocity $\mathbf{v}$. Furthermore, neglecting birth-death processes, the following definition can be introduced:

$$\mathcal{F}_i[\mathbf{f}](t,\mathbf{x},\mathbf{v}) := \mathcal{Q}_i[\mathbf{f},\mathbf{f}](t,\mathbf{x},\mathbf{v}) + \mathcal{K}_i(t,\mathbf{x},\mathbf{v}),$$

where functionals $\mathcal{Q}_i$ and $\mathcal{K}_i$ model, respectively, the net flux of individuals of population i through the volume element $d\mathbf{x}d\mathbf{v}$ centered in $(\mathbf{x},\mathbf{v})$ at time $t\in\mathbb{R}^+$ due to velocity changes mediated and not mediated by interactions.

2.2.1 Mathematical models

Focusing on the dynamics of one population only, i.e. $I=1$ and $\mathbf{f}(t,\mathbf{s}) = f(t,\mathbf{s})$, as well as taking advantage of the considerations drawn in [35] and reference therein, we can define $\mathcal{Q}[f](t,\mathbf{x},\mathbf{v})$ as a Boltzmann-type integral operator and make use of a velocity-jump formalism to define $\mathcal{K}(t,\mathbf{x},\mathbf{v})$:

$$\begin{aligned}\mathcal{Q}[f,f](t,\mathbf{x},\mathbf{v}) \quad &:= \quad \int_V\int_V Q(\mathbf{v}|\mathbf{v}_*,\mathbf{v}^*) f(t,\mathbf{x},\mathbf{v}_*) f(t,\mathbf{x},\mathbf{v}^*) d\mathbf{v}_* d\mathbf{v}^* + \\ &- \quad \int_V\int_V Q(\mathbf{v}^*|\mathbf{v}_*,\mathbf{v}) f(t,\mathbf{x},\mathbf{v}_*) f(t,\mathbf{x},\mathbf{v}) d\mathbf{v}_* d\mathbf{v}^*\end{aligned} \tag{2.10}$$

$$\mathcal{K}(t,\mathbf{x},\mathbf{v}) := \int_V K(\mathbf{v}|\mathbf{v}_*) f(t,\mathbf{x},\mathbf{v}_*) - K(\mathbf{v}_*|\mathbf{v}) f(t,\mathbf{x},\mathbf{v}) d\mathbf{v}_*, \tag{2.11}$$

with

$$\int_V \mathcal{F}[f](t,\mathbf{x},\mathbf{v}) d\mathbf{v} = 0, \quad \forall\, \mathbf{x}\in X \text{ and } \forall\, t\in\mathbb{R}^+, \tag{2.12}$$

so that, under assumption

$$\int_V f(t=0,\mathbf{x},\mathbf{v}) d\mathbf{v} = \varrho(t=0,x) = 1, \tag{2.13}$$

we have

$$\int_V f(t,\mathbf{x},\mathbf{v}) d\mathbf{v} = \varrho(t,x) = 1, \quad \forall\, t\in\mathbb{R}^+. \tag{2.14}$$

In the above definitions:

- interaction kernel $Q(\mathbf{v}|\mathbf{v}_*,\mathbf{v}^*)$ describes the probability that an individual moving with velocity $\mathbf{v}_*$ acquire velocity $\mathbf{v}$ after a short range interaction with an individual moving with velocity $\mathbf{v}^*$;

- scattering kernel $K(\mathbf{v}|\mathbf{v}_*)$ gives the rate of spontaneous turning from velocity $\mathbf{v}_*$ to velocity $\mathbf{v}$;

- analogous considerations hold for $Q(\mathbf{v}^*|\mathbf{v}_*, \mathbf{v})$ and $K(\mathbf{v}_*|\mathbf{v})$.

If changes in velocity mediated by interactions can be neglected and the system is exposed to an additional field $c(t, \mathbf{x})$ that influences the orientation of the individuals' motion, we can follow [18] and focus on nonlinear transport-scattering operators in the form given hereafter:

$$\mathcal{F}[f](t, \mathbf{x}, \mathbf{v}) := \int_V K(c(t, \mathbf{x}); \mathbf{v}|\mathbf{v}_*) f(t, \mathbf{x}, \mathbf{v}_*) - K(c(t, \mathbf{x}); \mathbf{v}_*|\mathbf{v}) f(t, \mathbf{x}, \mathbf{v}) d\mathbf{v}_*, \tag{2.15}$$

where the scattering kernel K now depends also on time and position through a nonlocal dependency upon function c, whose evolution can be modeled by means of an additional elliptic or parabolic equation. Identities (2.12)-(2.14) apply to this case as well.

2.2.2 Asymptotics

From a formal standpoint, the integro-differential models resulting from the coupling of Eq.(2.9) with definitions (2.10) and (2.11), or definition (2.15), are kinetic models of Boltzmann-type, which have been originally introduced for the study of moderately rarefied gases. The derivation of macroscopic models (i.e. evolution equations for $\varrho(t, \mathbf{x})$) from kinetic models is a classical topic and an introduction to the mathematical aspects of Boltzmann-type equations and their macroscopic limits is given in [59, 70] and references therein. Focusing on transport-scattering models, a small parameter $\varepsilon > 0$ modeling the transport/scattering ratio can be introduced, so that, under a diffusion scaling of time and position

$$f_\varepsilon(t, \mathbf{x}, \mathbf{v}) = f\left(\varepsilon t, \frac{\mathbf{x}}{\varepsilon}, \mathbf{v}\right), \tag{2.16}$$

Eq.(2.9) can be recast as follows

$$\partial_t f_\varepsilon(t, \mathbf{x}, \mathbf{v}) + \frac{\mathbf{v}}{\varepsilon} \cdot \nabla_{\mathbf{x}} f_\varepsilon(t, \mathbf{x}, \mathbf{v}) = \frac{1}{\varepsilon^2} \mathcal{F}[f_\varepsilon](t, \mathbf{x}, \mathbf{v}), \tag{2.17}$$

and macroscopic equations can be recovered in the limit $\varepsilon \to 0$ (i.e. assuming that the scattering part dominates transport). With reference to complex biological systems, drift-diffusion limits have been used, for instance, in the context of chemotaxis (i.e. the phenomenon whereby bacteria and cells direct their movements according to a field defined by the concentration of certain chemicals in their environment). See, for instance, [60] and related references. In particular, a rigorous derivation of the celebrated Keller-Segel model [41, 58] starting from a kinetic transport-scattering model for chemotaxis has been presented in [18].

2.2.3 Numerics

Focusing on bi-dimensional space domains, i.e. $d_x = 2$ and $\mathbf{x} = (x, y)$, velocities can be approximated in polar coordinates as follows:

$$\mathbf{v}(t) = \begin{pmatrix} v_x(t) \\ v_y(t) \end{pmatrix} = v_0 \begin{pmatrix} \cos\theta(t) \\ \sin\theta(t) \end{pmatrix}. \tag{2.18}$$

Approximation (2.18) implicitly relies on the assumption that the velocity modulus is constant and equal to v_0. If space and angular variables have been discretized, i.e. sets $\{(x_k, y_k)\}_k$ and $\{(\theta_l)\}_l$ have been defined, and suitable boundary conditions have been introduced, time splitting schemes can be adopted to numerically solve the Cauchy Problems linked to kinetic-like equations as the aforementioned ones. The advection term can be approximated in conservative form using flux-limiting schemes (see, for instance, [46]) and standard integration schemes can be used to compute the integral terms. In this way, a set of ordinary differential initial value problems is constructed, one for each $f(t, x_k, y_k, \theta_l)$, which can be solved using standard methods for ODEs (see, for instance, [45]).

2.3 Populations structured in opinion

Mathematical models for structured population in the context of opinion formation rely on the idea that the state of each individual can be identified with a single variable standing for the opinion with respect to a certain statement (i.e. $\mathbf{s} := s$), whose rate of evolution with respect to time can be set equal to zero, i.e.

$$\Gamma(s) = 0, \quad \forall\, s \in S,$$

so that Eq.(1.5) can be rewritten as follows:

$$\partial_t f_i(t, s) = \mathcal{F}_i[\mathbf{f}](t, s) \tag{2.19}$$

with

$$\mathcal{F}_i[\mathbf{f}](t, s) := \mathcal{Q}_i[\mathbf{f}, \mathbf{f}](t, s) + \mathcal{K}_i(t, s),$$

where functionals $\mathcal{K}_i$ and $\mathcal{Q}_i$ model, respectively, the net flux of individuals of population i through the volume element ds centered in s at time $t \in \mathbb{R}^+$ due, respectively, to spontaneous and mediated by interactions opinion changes.

2.3.1 Mathematical models

Here we focus on one single population where spontaneous changes of opinion do not occur. Furthermore, we assume opinions to evolve through repeated pairwise interactions involving only individuals at a distance smaller than a threshold value $R \in \mathbb{R}^+$, i.e. the so-called bound of confidence, that tend to average their current opinions, i.e. we focus on compromise models. In this case, setting

$$S := [-\sigma_1; \sigma_2] \subset \mathbb{R}, \quad \text{with} \quad \sigma_{1,2} \in \mathbb{R}^+,$$

we can follow, for instance, [1, 12, 24, 49, 68] and use the below definition

$$\begin{aligned}\mathcal{Q}[f,f](t,s) \quad &:= \quad \int_S\int_S \eta(s_*,s^*;R)Q(s|s_*,s^*)f(t,s_*)f(t,s^*)ds_*ds^* + \\ &- \quad \int_S\int_S \eta(s_*,s;R)Q(s^*|s_*,s)f(t,s_*)f(t,s)ds_*ds^*, \qquad (2.20)\end{aligned}$$

where:

- $\eta(s_*,s^*;R)$ is the interaction rate between a couple of agents expressing opinions s_* and s^*, which can be defined as

$$\eta(s_*,s^*;R) := \mathbf{1}_{\{|s_*-s^*|\leq R\}}, \qquad \eta(s_*,s^*;R) = \eta(s^*,s_*;R) \qquad (2.21)$$

  where $\mathbf{1}$ is the indicator function;

- interaction kernel $Q(s|s_*,s^*)$ describes the probability that individuals with opinion s_* start to express opinion s due to interactions with individuals of opinion s^* and it can be defined as

$$Q(s|s_*,s^*) := \delta\left(s - \frac{s_*+s^*}{2}\right), \qquad \int_S Q(s|s_*,s^*)ds = 1, \qquad (2.22)$$

  where $\delta(\cdot)$ is the Dirac's delta distribution;

- analogous considerations hold for $\eta(s_*,s;R)$ and $Q(s^*|s_*,s)$.

The average opinion $\bar{s}$ at time t can be computed as the first moment of $f(t,s)$, i.e.

$$\bar{s}(t) = \frac{\int_S sf(t,s)ds}{\rho(t)}.$$

2.3.2 Asymptotics

Model (2.20) belongs to a large class of equations for continuous structured populations, or one dimensional Boltzmann-like kinetic equations, that can be derived from individual based models in the limit of large number of agents. Asymptotic analysis can be developed in the limit $t \to \infty$ (i.e. in the limit of large time), with the aim of proving the convergence (in a suitable weak sense) of function f to a distribution f^∞ that concentrate as a sum of Dirac masses, that is

$$f^\infty(s) := \sum_{n=1}^N \varrho_n \delta(s-\hat{s}_n), \quad |\hat{s}_a - \hat{s}_b| > R, \quad \forall\,(\hat{s}_a,\hat{s}_b) \in \{\hat{s}_n\}_{n=1}^N, \quad a \neq b.$$

From a socio-economic perspective, this kind of convergence results provide a possible mathematical formalization for the emergence of a steady compromise. In fact, the population condenses, across time, into a finite set of distinct and noninteracting opinion clusters.

Several previous works have been devoted to study the existence of such equilibrium configurations, see for instance [1, 12, 24, 49, 68] and references therein, even in a discrete setting [9]. With particular reference to the model under consideration, with $\sigma_1 = \sigma_2 = \sigma \in \mathbb{R}^+$:

- conservation of the total mass and the average opinion has been proved for all values of R;
- it has been proved that, if $R \geq 2\sigma$ (i.e. all the individuals interact among themselves), the opinion distribution converges to a single cluster located in $\bar{s}(t = 0)$;
- it has been verified, by means of numerical simulations, that for $R < 2\sigma$ the opinion distribution may not condense into a single cluster, but rather it might evolve into some isolated clusters separated by distances larger than R.

2.3.3 Numerics

The Cauchy Problems linked to opinion-structured equations can be numerically solved through spectral collocation methods (see, for instance, [17]). Roughly speaking, a suitable discrete set of collocation points $\{\mathbf{s}_k\}_k \in S$ is first introduced; after that, focusing on one single population, the f function is interpolated by means of *sinc* functions, that is

$$f(t, s) \approx \sum_k f(t, s_k) sinc(s - s_k),$$

and the integral terms are approximated by means of algebraic weighted sums in the nodal points of the discretization. The evaluation of the opinion-structure equation in each node and the enforcing of the initial conditions allow the conversion of the original integro-differential initial value problem into a set of initial value problems for ordinary differential equations, which describes the evolution of each $f(t, s_k)$. These ordinary differential initial value problems can be solved by means of standard methods for ODEs (see, for instance, [45]).

Part III

Models for Living Species

Introduction

We will now discuss in a little more
detail the Struggle for Existence
C. Darwin, The Origin of Species

This parts deals with phenotype-structured equations for the dynamics of living species. In particular,

- Chapter 3 presents a class of integro-differential equations arising in evolutionary biology to model the dynamics of specialist and generalist species related by facultative mutualistic interactions. These equations are able to reproduce Darwinian evolution and speciation.

- Chapter 4 is about phenotype structured equations modeling the dynamics of species related by predation. The effects of mutations, proliferation through asexual reproduction and competition for resources are included in the model, which can mimic the formation of evolutionary branching patterns.

- Chapter 5 introduces a multi-dimensional integro-differential equation for the dynamics of habitat-specialist and habitat-generalist species endangered by habitat shrinking and global warming. This equation can be used to describe the evolution of endangered species under different hypothetical scenarios.

Chapter 3

Asymptotic dynamics in continuous structured populations with mutations, competition and mutualism [A5]

3.1 Motivations and models

This paper deals with a class of integro-differential equations arising in evolutionary biology to model the dynamics of specialist and generalist species related by facultative mutualistic interactions (i.e. the growth of a population affects the proliferation of individuals in the other one, although both species can survive even in the absence of the other one) [36, 54]. Generalist species are able to consume a wide range of nutrients, while specialist species concentrate on a narrow band of resources [50]. The effects of mutations, proliferation through asexual reproduction and competition for resources are included in the model here considered.

In particular, the reference system is defined by one structured subpopulation collecting specialist individuals and one unstructured subpopulation composed of generalist individuals, which are labeled by indexes $i = 1$ and $i = 2$, respectively. Subpopulation $i = 1$ is structured by a continuous phenotypic trait $s \in S \subset \mathbb{R}$ related to the ability to ingest specific resources. Interval S is compact, i.e. $S := [0, 1]$, and, since mutations are assumed to be small and to occur on a longer time scale than proliferation, a parameter ε is introduced to model the ratio between these time scales as well as the average size of mutations.

The states of the two subpopulations are characterized by functions

$$f_1 = f_1(t,s) : \mathbb{R}^+ \times S \to \mathbb{R}^+, \qquad n_2 = n_2(t) : \mathbb{R}^+ \to \mathbb{R}^+,$$

and the dynamics of the system is described through the following Cauchy Problem

$$\begin{cases} \partial_t \mathbf{h}(t,s) = \mathcal{H}[\mathbf{h}](t,s), \quad (t,s) \in (0,T] \times S \\ \\ \mathbf{h}(0,s) = \mathbf{h}^0(s), \end{cases} \tag{3.1}$$

where

$$\mathbf{h}(t,s) = (f_1(t,s), n_2(t)),$$
$$\mathbf{h}^0(s) = (f_1^0(s), n_2^0), \quad f_1^0(s) \in L^1(S), \quad f_1^0(s) > 0 \text{ a.e. on } S, \quad n_2^0 \in \mathbb{R}^+$$

and $\mathcal{H}[\mathbf{h}]$ is componentwise defined by the integro-differential equations given hereafter:

$$\begin{aligned} \partial_t f_1(t,s) &= \underbrace{\int_S M(s-s_*;\varepsilon) f_1(t,s_*) ds_* - f_1(t,s)}_{\text{mutations and renewal}} + \underbrace{\kappa_1(s) n_2(t) f_1(t,s)}_{\text{mutualism}} \\ &+ \underbrace{f_1(t,s)\left(\beta_1(s) - \int_S \mu(s,s^*) f_1(t,s^*) ds^*\right)}_{\text{proliferation and competition}} \end{aligned} \tag{3.2}$$

$$d_t n_2(t) = \underbrace{n_2(t) \int_S \kappa_2(s^*) f_1(t,s^*) ds^*}_{\text{mutualism}} + \underbrace{\left(\beta_2 - \zeta n_2(t)\right) n_2(t)}_{\text{proliferation and competition}} .$$

With reference to Eqs. (3.2):

$$M(s-s_*;\varepsilon) := \begin{cases} \alpha\delta(s-(s_* \pm \varepsilon)) + (1-2\alpha)\delta(s-s_*), & \text{if } \varepsilon < s < 1-\varepsilon \\ \alpha\delta(s-(s_*-\varepsilon)) + (1-\alpha)\delta(s-s_*), & \text{if } 0 \le s \le \varepsilon \\ \alpha\delta(s-(s_*+\varepsilon)) + (1-\alpha)\delta(s-s_*), & \text{if } 1-\varepsilon \le s \le 1, \end{cases}$$

where $\alpha \in \mathbb{R}^+$, δ is the Dirac's delta distribution,

$$\beta_1 : S \to \mathbb{R}^+, \quad \beta_1 \in W^{2,\infty}(S), \quad \inf_s \beta_1(s) > 0, \quad \beta_2 \in \mathbb{R}^+, \tag{3.3}$$

$$\mu : S \times S \to \mathbb{R}^+, \quad \mu \in W^{2,\infty}(S \times S), \quad \inf_{s,s^*} \mu(s,s^*) > 0, \quad \zeta \in \mathbb{R}^+, \tag{3.4}$$

$$\kappa_i : S \to \mathbb{R}^+, \quad \kappa_i \in W^{2,\infty}(S), \quad \inf_s \kappa_i(s) > 0, \quad i = 1,2 \tag{3.5}$$

and

$$\kappa_1(s)\kappa_2(s^*) < \zeta\mu(s,s^*), \qquad \forall (s,s^*) \in S \times S. \tag{3.6}$$

The above definition for $M(s-s_*;\varepsilon)$ translates into mathematical terms the idea that mutations are small, i.e. only small variations in the phenotypic trait can occur from parent to offspring, while assumption (3.6) embodies the fact that proliferative phenomena due to mutualistic interactions occur with a lower rate than competition for resources.

3.2 Main results

Using standard fixed point arguments, we prove that the Cauchy Problem (4.1) is well-posed, in the sense of Hadamard, and admits a unique global in time solution.

Then, in order to capture the slow evolutionary process leading to substantial changes in the predominant traits, we use the following time rescaling

$$\mathbf{h}_\varepsilon(t,s) = \mathbf{h}\left(\frac{t}{\varepsilon}, s\right),$$

and rewrite Eqs. (3.1) as follows

$$\begin{cases} \varepsilon \partial_t \mathbf{h}_\varepsilon(t,s) = \mathcal{H}[\mathbf{h}_\varepsilon](t,s), \quad (t,s) \in (0,T] \times S \\ \\ \mathbf{h}(0,s) = \mathbf{h}^0(s), \end{cases} \tag{3.7}$$

with the aim of studying the asymptotic behavior, in the limit $\varepsilon \to 0$ (i.e. large times and small mutations), of the solution to the Cauchy Problem (3.1). In particular, after introducing the notation below

$$R_\varepsilon(t,s) := \beta_1(s)t + \kappa_1(s) \int_0^t n_{2\varepsilon}(z) - \int_S \mu(s,s^*) f_{1\varepsilon}(z,s^*) ds^* dz,$$

we show how an approach similar to the one proposed in [25] can be used to study the asymptotic behavior of the solution to the initial value problem (3.7):

Theorem 3.2.1 *There exist a subsequence of $f_{1\varepsilon}$, denoted again as $f_{1\varepsilon}$, and a subsequence of R_ε, denoted again as R_ε, such that:*

i) Establishing convergence.

$$f_{1\varepsilon} \rightharpoonup \hat{f}_1 \text{ on } \; w^* - L^\infty((0,T), M^1(S)), \quad \text{as } \varepsilon \to 0,$$
$$R_\varepsilon \to R \text{ uniformly in } \; [0,T] \times S, \quad \text{as } \varepsilon \to 0,$$

where $\hat{f}_1 \in L^\infty((0,T), M^1(S))$,

$$R(t,s) = \beta_1(s)t + \kappa_1(s) \int_0^t n_2(z) - \int_S \mu(s,s^*) \hat{f}_1(z,s^*) ds^* dz \tag{3.8}$$

and

$$R(t,s) \in W^{2,\infty}((0,T) \times S), \qquad \max_{s \in S} R(t,s) = 0, \qquad \forall\, t \in [0,T].$$

ii) Characterizing the support of the limit $\hat{f}_1$.

$$supp(\hat{f}_1(t,\cdot)) \neq \emptyset, \quad supp(\hat{f}_1(t,\cdot)) \subset R(t,\cdot)^{-1}(0), \quad \text{for a.e. } t \in [0,T].$$

iii) Identifying the limit $\hat{f}_1$.
If functions β_1 and κ_1 have a positive maximum attained, respectively, at some points $\{u_n\}_{n=1}^N$ and $\{w_n\}_{n=1}^M$, with $N, M \in \mathbb{N}$, then the measure $\hat{f}_1$ results as follows:

$$\hat{f}_1(t,s) = \sum_{n=1}^{N} \varrho_{\beta n}(t)\delta(s-u_n) + \sum_{n=1}^{M} \varrho_{\kappa n}(t)\delta(s-w_n), \quad \varrho_{\beta n}(t), \varrho_{\kappa n}(t) \geq 0. \tag{3.9}$$

A characterization of factors $\{\varrho_{\beta n}\}_{n=1}^N$ and $\{\varrho_{\kappa n}\}_{n=1}^M$ of (3.9) is provided by the following

Proposition 3.2.2 *If $N = M$ and $u_n = w_n$ for all n, then for any value of n:*

$$\varrho_{\beta n}(t) > 0 \quad \textit{and} \quad \varrho_{\kappa n}(t) > 0.$$

On the other hand, if $\mu(s, s^*)$ factorizes as $\mu(s, s^*) = \mu_1(s)\mu_2(s^*)$, with $\mu_1, \mu_2 \in W^{2,\infty}(S)$, $N \neq M$, $\{u_n\}_{n=1}^N \cap \{w_n\}_{n=1}^M = \emptyset$ and

$$\frac{\beta_1(u_n)}{\mu_1(u_n)} = \frac{\kappa_1(w_n)}{\mu_1(w_n)}, \qquad \forall u_n \in \{u_n\}_{n=1}^N, \quad \forall w_n \in \{w_n\}_{n=1}^M,$$

there exists T_ℓ such that one of these conditions is verified:

- if $\zeta < \beta_2$, then

$$\varrho_{\beta n}(t) = 0 \quad \textit{and} \quad \varrho_{\kappa n}(t) \geq 0, \qquad \forall t > T_\ell,$$

for any value of n;

- if $\zeta \geq \beta_2 + C_3\|\kappa_2\|_{L^\infty(S)}$, with

$$C_3 := \max\left(\frac{\|\beta_1\|_{L^\infty(S)} + \beta_2/\zeta\|\kappa_1\|_{L^\infty(S)}}{\inf|(\kappa_1\kappa_2)/\zeta - \mu|}, \|f_1^0\|_{L^1(S)} \right),$$

then

$$\varrho_{\beta n}(t) \geq 0 \quad \textit{and} \quad \varrho_{\kappa n}(t) = 0, \qquad \forall t > T_\ell,$$

for any value of n.

In order to illustrate analytical results, we numerically solve the Cauchy Problem (3.1) with

$$f_1^0(s) := C_1^0 e^{\frac{-(s-0.5)^2}{0.01}}, \qquad n_2^0 := C_2^0, \tag{3.10}$$

where C_1^0 and C_2^0 are positive real constants such that

$$\int_S f_1^0(s)\, ds + n_2^0 = 1.$$

We set $\varepsilon = 0.001$ (i.e. $\varepsilon \to 0$),

$$\mu(s, s^*) = \mu_1(s)\mu_2(s^*), \qquad \mu_1(s) := \mu^C \in \mathbb{R}^+, \qquad \mu_2(s) := 1, \tag{3.11}$$

$$\kappa_2(s) := C_M \, e^{-\frac{[(s-0.5)^2]}{0.3}}, \tag{3.12}$$

$$\beta_1(s) := C_M \, e^{-\frac{[(s-0.15)^2+(s-0.85)^2]}{0.03}}, \quad \kappa_1(s) := C_M \, e^{-\frac{[(s-0.35)^2+(s-0.65)^2]}{0.03}}, \tag{3.13}$$

with $C_M \in \mathbb{R}^+$. Numerical computations are performed in MATLAB by means of a collocation method with 200 points on $[0, 1]$. Interval $[0, T]$ is selected as time domain, where $T = 200$ is an integer multiple of the unit time $dt = 0.005$.

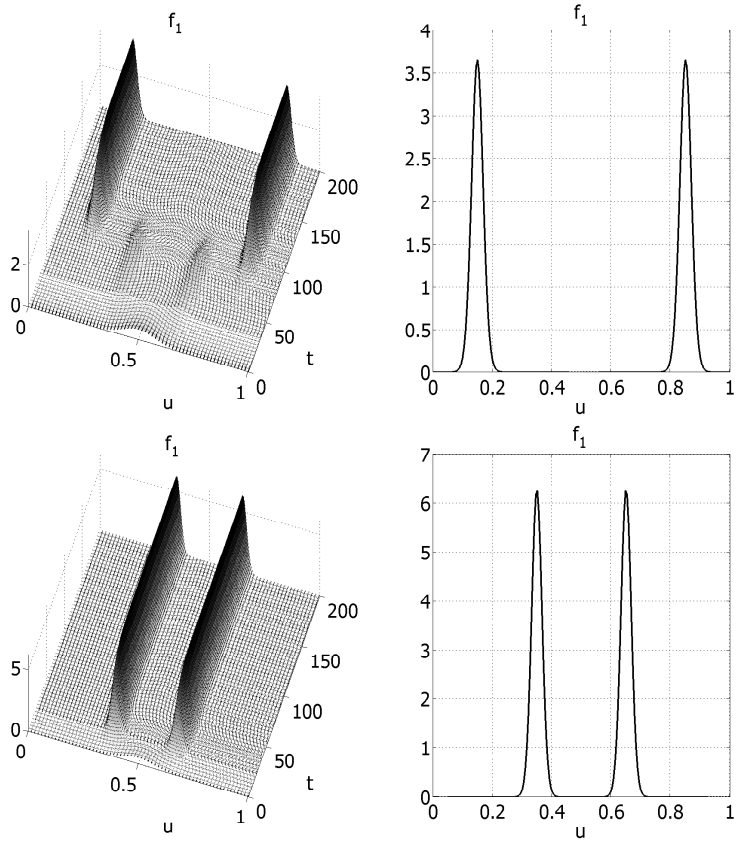

Figure 3.1: **Top panel.** Trends of $f_1(t, s)$ in the limit $\varepsilon \to 0$ under assumptions (3.13), with $\zeta \geq \beta_2 + C_3 C_M$, for $t \in [0, 200]$ (left) and $t = 200$ (right). **Bottom panel.** Trends of $f_1(t, s)$ in the limit $\varepsilon \to 0$ under assumptions (3.13), with $\zeta < \beta_2$, for $t \in [0, 200]$ (left) and $t = 200$ (right).

Chapter 4

Evolutionary branching patterns in predator-prey structured populations [A10]

4.1 Motivations and model

Selective pressures exerted by the surrounding environment can make a population initially composed of individuals expressing the same phenotype (i.e. a phenotypically monomorphic population) to split into two or more distinct populations, or phenotypic clusters. Such a dynamical process may occur several times along the history of a living specie leading to the formation of evolutionary branching patterns.

Predator-prey ecosystems represent, among others, a natural context where evolutionary branching processes may arise. In fact, preys are parts of the predators' environment and, in turn, predators shape the environment around the preys, so that a change in the relative distribution over the phenotypic traits of the preys can induce a change in the predominant traits within the predators' population. For instance, one can dynamically observe the selection for those preys that are able to escape predation and those predators whose phenotypic traits allow them to catch a large number of preys.

Moving from such observation, this paper deals with a class of integro-differential equations modeling the dynamics of species related by predation. The effects of mutations, proliferation through asexual reproduction and competition for resources are included in the model here considered, which can mimic the formation of evolutionary branching patterns.

The reference system is defined by two structured subpopulations labelled by indexes $i = 1, 2$, which collect, respectively, predators and preys. The two

subpopulations are structured by a continuous variable $s \in S := [0,1]$. In subpopulation $i = 1$, variable s stands for a certain phenotypic trait expressed by the preys, while in subpopulation $i = 2$ the same variable refers to the trait of the preys that predators are mainly able to catch. Since mutations are assumed to be small and to occur on a longer time scale than proliferation, a parameter ε is introduced to model the ratio between these time scales as well as the average size of mutations.

The states of the two subpopulations are characterized by functions

$$f_1 = f_1(t,s) : \mathbb{R}^+ \times S \to \mathbb{R}^+, \qquad f_2 = f_2(t,s) : \mathbb{R}^+ \times S \to \mathbb{R}^+,$$

and the dynamics of the whole system is described through the following Cauchy Problem

$$\begin{cases} \partial_t \mathbf{f}(t,s) = \mathcal{F}[\mathbf{f}](t,s), \quad (t,s) \in (0,T] \times S \\ \\ \mathbf{f}(0,s) = \mathbf{f}^0(s), \end{cases} \tag{4.1}$$

where

$$\mathbf{f}(t,s) = (f_1(t,s), f_2(t,s)),$$
$$\mathbf{f}^0(s) = (f_1^0(s), f_2^0(s)), \quad f_1^0(s), f_2^0(s) \in L^1(S), \quad f_1^0(s), f_2^0(s) > 0 \text{ a.e. on } S$$

and $\mathcal{F}[\mathbf{f}]$ is componentwise defined by the integro-differential equations given hereafter:

$$\begin{aligned} \partial_t f_1(t,s) &= \underbrace{\int M(s-s_*;\varepsilon) f_1(t,s_*) du_* - f_1(t,s)}_{\text{mutations and renewal}} \\ &+ \underbrace{f_1(t,s)\left(\kappa_1 - \mu_1 \int f_1(t,s^*) du^*\right)}_{\text{proliferation and competition}} - \underbrace{f_1(t,s) \int \eta(s^*-s) f_2(t,s^*) ds^*}_{\text{death through predation}} \end{aligned} \tag{4.2}$$

$$\begin{aligned} \partial_t f_2(t,s) &= \underbrace{\int_S M(s-s_*;\varepsilon) f_2(t,s_*) ds_* - f_2(t,s)}_{\text{mutations and renewal}} \\ &+ \underbrace{f_2(t,s)\left(\kappa_2 - \mu_2 \int f_2(t,s^*) du^*\right)}_{\text{proliferation and competition}} + \underbrace{f_2(t,s) \int \eta(s_*-s) f_1(t,s_*) ds_*}_{\text{proliferation through predation}} . \end{aligned}$$

With reference to Eqs. (4.2):

$$M(s-s_*;\varepsilon) := \begin{cases} \alpha\delta(s-(s_* \pm \varepsilon)) + (1-2\alpha)\delta(s-s_*), & \text{if } \varepsilon < s < 1-\varepsilon \\ \alpha\delta(s-(s_*-\varepsilon)) + (1-\alpha)\delta(s-s_*), & \text{if } 0 \le s \le \varepsilon \\ \alpha\delta(s-(s_*+\varepsilon)) + (1-\alpha)\delta(s-s_*), & \text{if } 1-\varepsilon \le s \le 1, \end{cases}$$

where δ is the Dirac's delta distribution, $\alpha \in \mathbb{R}^+$,

$$\kappa_1, \kappa_2 \in \mathbb{R}^+, \qquad \kappa_2 < \kappa_1, \tag{4.3}$$

$$\mu_1, \mu_2 \in \mathbb{R}^+, \qquad \mu_1 \geq 1, \qquad \mu_2 \geq 1, \tag{4.4}$$

$$\eta : S \times S \to \mathbb{R}^+, \quad \eta \in W^{2,\infty}(S \times S), \quad \frac{d}{dw}\eta(w) \leq 0. \tag{4.5}$$

The above definition for $M(s - s_*; \varepsilon)$ translates into mathematical terms the idea that mutations are small, i.e. only small variations in the phenotypic trait can occur from parent to offspring. Furthermore, assumption (4.3) mimics a biological scenario where the predators' proliferation mainly occurs through the predation of preys rather than through the intake of other resources, while assumption (4.4) embodies the fact that competition for resources among individuals of the same subpopulation is quite intense.

4.2 Main results

Following the strategy of the proof proposed in [8] for a different class of integro-differential equations, we prove that the Cauchy Problem (4.1) is well-posed, in the sense of Hadamard, and admits a unique global in time solution.

Then, in order to capture the slow evolutionary process leading to substantial changes in the predominant traits, we use the following time rescaling

$$\mathbf{f}_\varepsilon(t, s) = \mathbf{f}\left(\frac{t}{\varepsilon}, s\right),$$

and rewrite Eqs. (4.1) as follows

$$\begin{cases} \varepsilon \dfrac{\partial}{\partial t}\mathbf{f}_\varepsilon(t, s) = \mathcal{F}[\mathbf{f}_\varepsilon](t, s), \quad (t, s) \in (0, T] \times S \\ \\ \mathbf{f}(0, s) = \mathbf{f}^0(s), \end{cases} \tag{4.6}$$

with the aim of studying the asymptotic behavior, in the limit $\varepsilon \to 0$ (i.e. large times and small mutations), of the solution to the Cauchy Problem (4.1). In particular, after introducing the notations below

$$\begin{aligned} R_{1\varepsilon}(t, s) &= \kappa_1 t - \mu_1 \int_0^t \int_S f_{1\varepsilon}(z, s^*) ds^* - (\eta * f_{2\varepsilon})(z, s) dz \\ R_{2\varepsilon}(t, s) &= \kappa_2 t - \mu_2 \int_0^t \int_S f_{2\varepsilon}(z, s^*) ds^* + (\eta * f_{1\varepsilon})(z, s) dz, \end{aligned}$$

we show how an approach similar to the one proposed in [25] can be used to study the asymptotic behavior of the solution to the initial value problem (4.6):

Theorem 4.2.1 *Let $supp(f_1^0) = supp(f_2^0)$ and assume*

$$\|f_1^0\|_{L^1(S)} < \frac{\kappa_1}{\mu_1}, \quad \|f_2^0\|_{L^1(S)} < \frac{\kappa_2 + \|\eta\|_{L^\infty(S \times S)} \, \|f_1^0\|_{L^1(S)}}{\mu_2}. \tag{4.7}$$

Then, there exist a subsequence of $f_{i\varepsilon}$, denoted again as $f_{i\varepsilon}$, and a subsequence of $R_{i\varepsilon}$, denoted again as $R_{i\varepsilon}$, such that:

i) Establishing convergence.

$$f_{i\varepsilon} \rightharpoonup \hat{f}_i \text{ on } w^* - L^\infty((0,T), M^1(S)), \quad \text{as } \varepsilon \to 0,$$
$$R_{i\varepsilon} \to R_i \text{ uniformly in } [0,T] \times S, \quad \text{as } \varepsilon \to 0,$$

where $\hat{f}_i \in L^\infty((0,T), M^1(S))$,

$$\begin{aligned} R_1(t,s) &= \kappa_1 t - \mu_1 \int_0^t \int_S \hat{f}_1(z,s^*)ds^* - (\eta * \hat{f}_2)(z,s)dz, \\ R_2(t,s) &= \kappa_2 t - \mu_2 \int_0^t \int_S \hat{f}_2(z,s^*)ds^* + (\eta * \hat{f}_1)(z,s)dz \end{aligned} \tag{4.8}$$

and

$$\max_{s\in S} R_i(t,s) = 0, \qquad \forall\, t \in [0,T],$$

for $i = 1, 2$.

ii) Characterizing the support of the limits $\hat{f}_1$ *and* $\hat{f}_2$.

Let us define $\Omega_i(t) := R_i(t,\cdot)^{-1}(0)$. *Then, the following conditions hold true for a.e.* $t \in [0,T]$

$$supp(\hat{f}_i(t,\cdot)) \neq \emptyset, \quad supp(\hat{f}_i(t,\cdot)) \subseteq \Omega_i(t), \quad i = 1, 2,$$

where:

$$\begin{aligned} \Omega_1(t) &= \left\{\omega \in S \mid \min_s I_1(t,s) = I_1(\omega,t)\right\}, \\ \Omega_2(t) &= \left\{\omega \in S \mid \max_s I_2(t,s) = I_2(\omega,t)\right\} \end{aligned}$$

and

$$I_1(t,s) := \int_0^t (\eta * \hat{f}_2)(z,s)dz, \qquad I_2(t,s) := \int_0^t (\eta * \hat{f}_1)(z,s)dz. \tag{4.9}$$

In order to illustrate analytical results, we numerically solve, under different parameter settings, the Cauchy Problem (4.1) with

$$f_1^0(s) = f_2^0(s) = C^0 e^{\frac{-(s-0.5)^2}{\varepsilon}}, \tag{4.10}$$

where C^0 is a positive real constant such that

$$\int_S f_1^0(s) + f_2^0(s)\, ds = 1.$$

We set $\varepsilon = 0.001$ (i.e. $\varepsilon \to 0$),

$$\alpha = 0.5, \quad \kappa_1 = 0.8, \quad \kappa_2 = 0.4, \quad \mu_1 = \mu_2 = 1, \tag{4.11}$$

and define function η as

$$\eta(s, s^*) := e^{-\frac{(s-s^*)^2}{\varepsilon}}. \tag{4.12}$$

Numerical computations are performed in MATLAB by means of a collocation method with 200 points on $[0, 1]$. Interval $[0, T]$ is selected as time domain, where $T = 700$ is an integer multiple of the unit time $dt = 0.005$.

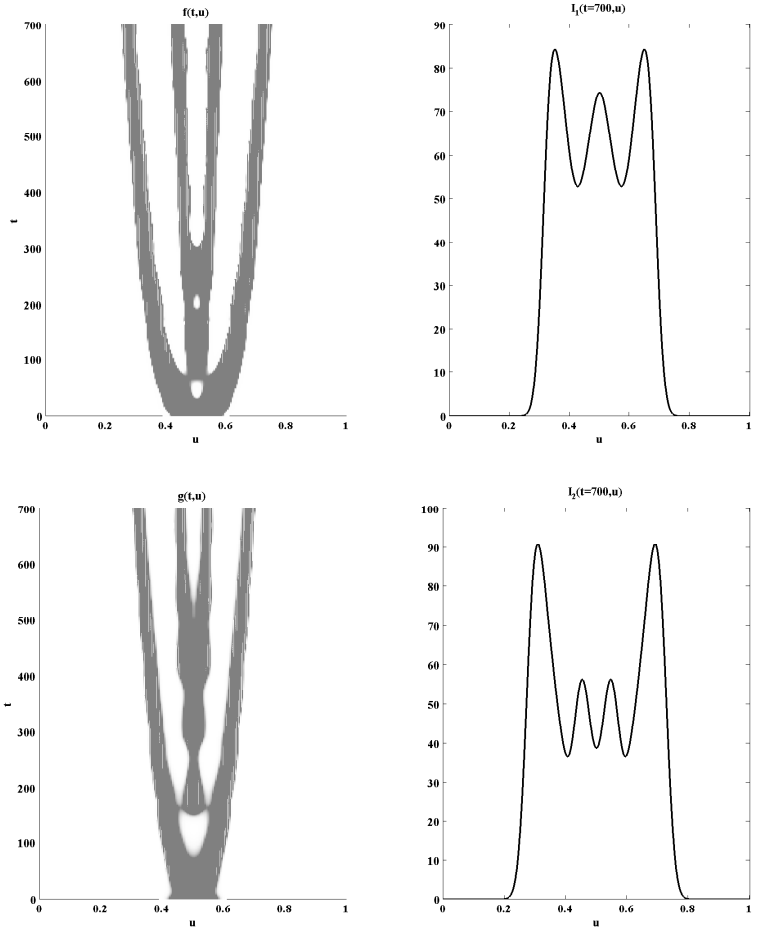

Figure 4.1: **Left panel.** Dynamics of $f_1(t, s)$ (top) and $f_2(t, s)$ (bottom) for $t \in [0, 700]$, in the limit $\varepsilon \to 0$, with initial data (4.10) and parameter setting (4.11). **Right panel.** Trend of $I_1(t, s)$ (top) and $I_2(t, s)$ (bottom) at t=700, in the limit $\varepsilon \to 0$, under the same parameter setting.

Chapter 5

Asymptotic dynamics in populations structured by sensitivity to global warming and habitat shrinking [A11]

5.1 Motivations and model

The rise of average temperatures and the spread of human urbanization are endangering the survival of habitat-specialist species [32]. In fact, in contrast to habitat-generalists, which are more adapted to reduced biodiversity and new environmental conditions, habitat-specialists are characterized by a stronger sensitivity to nutrition variation. Therefore, they are often forced to move poleward by global warming, in order to follow specific subsistence resources. Moreover, generalist species may take advantage of man's proximity and they are able to live both in interiors and edges of habitat-patches. On the other hand, specialist species used to live in the interior areas of patches and avoid edges, since they are disturbed by those external factors that usually come along with civilization.

This paper presents a possible modeling strategy to translate into mathematical terms the idea that habitat shrinking affects the growth of individuals by altering bio-diversity and space availability, while global warming diminishes available resources, thus intensifying the competition among individuals.

The reference system is structured by two continuous variables

$$\mathbf{u} \in U := [a_U, b_U]^k \subset \mathbb{R}^k \quad \text{and} \quad \mathbf{w} \in W := [a_w, b_w]^l \subset \mathbb{R}^l,$$

with

$$-\infty < a_U, b_U, a_W, b_W < \infty, \quad \mathbb{Z} \ni k, l \geq 1, \quad \mathbf{s} := (\mathbf{u}, \mathbf{w}) \in S, \quad S := U \times W,$$

which represent the sensitivity to, respectively, habitat shrinking and global warming. Habitat-generalists are assumed to be characterized by $\mathbf{u}$ and $\mathbf{w}$ close, respectively, to a_U and a_W, whereas habitat-specialists are identified by $\mathbf{u}$ and $\mathbf{w}$ close, respectively, to b_U and b_W. The effects of mutations, proliferation through asexual reproduction and competition for resources are included in the model. Since mutations are assumed to be small and to occur on a longer time scale than proliferation, a small parameter ε is introduced to model the ratio between these time scales as well as the average size of mutations.

The density of individuals with a sensitivity level $\mathbf{s}$ at time t is modeled by the real function $f(t, \mathbf{s}) \geq 0$ that satisfies the Cauchy Problem given hereafter

$$\begin{cases} \partial_t f(t, \mathbf{s}) = \mathcal{F}[f](t, \mathbf{s}), & (t, \mathbf{s}) \in \mathbb{R}^+ \times S \\ f(0, \mathbf{s}) = f^0(\mathbf{s}) \in L^1(S), & f^0(\cdot) > 0 \text{ a.e. on } S. \end{cases} \tag{5.1}$$

Functional $\mathcal{F}$ is defined as follows:

$$\begin{aligned} \mathcal{F}[f](t, \mathbf{s}) \quad := \quad & \underbrace{\alpha \int_U M_U(\mathbf{u} - \mathbf{u}_*; \varepsilon) f(t, \mathbf{u}_*, \mathbf{w}) d\mathbf{u}_* - \alpha f(t, \mathbf{u}, \mathbf{w})}_{\text{mutations and renewal related to habitat shrinking sensitivity}} \\ + \quad & \underbrace{\beta \int_W M_W(\mathbf{w} - \mathbf{w}_*; \varepsilon) f(t, \mathbf{u}, \mathbf{w}_*) d\mathbf{w}_* - \beta f(t, \mathbf{u}, \mathbf{w})}_{\text{mutations and renewal related to global warming sensitivity}} \\ + \quad & \underbrace{\kappa(t, \mathbf{u}) - \mu(t, \mathbf{w}) \int_S f(t, \mathbf{s}) d\mathbf{s}}_{\text{proliferation and competition}}, \end{aligned} \tag{5.2}$$

where:

$$M_U(\mathbf{u} - \mathbf{u}_*; \varepsilon) := \prod_{i=1}^{k} M_U(u_i - u_{*i}; \varepsilon), \tag{5.3}$$

with

$$M_U(u_i - u_{*i}; \varepsilon) := \begin{cases} \delta(u_i - (u_{*i} \pm \varepsilon)) - \delta(u_i - u_{*i}), & \text{if } a_U + \varepsilon < u_i < b_U - \varepsilon \\ \delta(u_i - (u_{*i} - \varepsilon)), & \text{if } a_U \leq u_i \leq a_U + \varepsilon \\ \delta(u_i - (u_{*i} + \varepsilon)), & \text{if } b_U - \varepsilon \leq u_i \leq b_U \end{cases}$$

for $i = 1, ..., k$, where δ is the Dirac's delta distribution, and analogous definitions apply to $M_W(\mathbf{w} - \mathbf{w}_*; \varepsilon)$,

$$\kappa(t, u) := \kappa_3 + \kappa_1(t)\kappa_2(u) > 0, \quad \mu(t, w) := \mu_3 + \mu_1(t)\mu_2(w) > 0, \tag{5.4}$$

with

$$\kappa_3, \mu_3 \geq 0, \quad \kappa_1, \mu_1 : [0, T] \to \mathbb{R}, \quad \kappa_1, \mu_1 \in W^{1,\infty}([0, T]), \tag{5.5}$$

$$\kappa_2 : U \to \mathbb{R}^+, \quad \kappa_2 \in W^{2,\infty}(U), \quad \mu_2 : W \to \mathbb{R}^+, \quad \mu_2 \in W^{2,\infty}(W). \tag{5.6}$$

Eq. (5.2) relies on the assumption that mutations in the $\mathbf{u}$ and $\mathbf{w}$ traits are independent from one another, while the definitions of M_U and M_W translate into mathematical terms the idea that mutations cause small changes in the sensitivity to habitat shrinking and global warming. Definitions (5.4) are based on the idea that habitat shrinking can be considered as an external pressure affecting the growth of individuals by altering bio-diversity and space availability, while global warming can be seen as acting over the competition among individuals by modifying the quantity of available resources [31, 32, 57]. In fact, functions $\kappa(t, \mathbf{u})$ and $\mu(t, \mathbf{w})$ model, respectively, the proliferation rate and death rate due to competition for resources of individuals with phenotypic expression $(\mathbf{u}, \mathbf{w})$ at time t. Furthermore, the selective forces exerted by habitat shrinking and global warming can evolve over time due, for instance, to human migratory fluxes or to oscillations in average temperatures. For this reasons, κ and μ are defined as functions of time.

5.2 Main results

Standard fixed point arguments can be used to show that Problem (5.1) is well-posed, in the sense of Hadamard, and admits a unique global in time solution.

In order to capture the slow evolutionary process leading to substantial changes in the predominant traits, we use the following time rescaling

$$f_\varepsilon(t, \mathbf{s}) = f\left(\frac{t}{\varepsilon}, \mathbf{s}\right),$$

and rewrite Problem (5.1) as follows

$$\begin{cases} \varepsilon \partial_t f_\varepsilon(t, \mathbf{s}) = \mathcal{F}[f_\varepsilon](t, \mathbf{s}), \quad (t, \mathbf{s}) \in (0, T] \times S \\ \\ f(0, \mathbf{s}) = f^0(\mathbf{s}), \end{cases} \tag{5.7}$$

with the aim of studying the asymptotic behavior of the solution in the limit $\varepsilon \to 0$ (i.e. large times and small mutations). Introducing the below notation

$$R(t, \mathbf{s}) := \int_0^t \kappa(z, \mathbf{u}) - \mu(z, \mathbf{w}) \int_S f(z, \mathbf{s}) d\mathbf{s}\, dz,$$

an approach similar to the one proposed in [25] can be used to demonstrate that f concentrates as a sum of Dirac masses in the maximum points of function $R(t, \cdot)$. A characterization of the concentration points can be developed, under some additional technical assumptions, as established by the following

Proposition 5.2.1 *If*

$$\kappa_3 = \mu_3 = 0, \quad \kappa_1(t) > 0, \ \forall\, t \in [0, T], \quad \mu_1(t) > 0, \ \forall\, t \in [0, T] \tag{5.8}$$

and

$$\max_{(\mathbf{u},\mathbf{w})\in U}\left(\kappa_2(\mathbf{u})\mu_2^{-1}(\mathbf{w})\right)=\kappa_2(\overline{\mathbf{u}}_n)\mu_2^{-1}(\underline{\mathbf{w}}_n),\quad \{(\overline{\mathbf{u}}_n,\underline{\mathbf{w}}_n)\}_{n=1}^N\in U, \tag{5.9}$$

then the measure $\hat{f}$ *results as follows:*

$$\hat{f}(t,\mathbf{u},\mathbf{w})=\sum_{n=1}^N \varrho_n(t)\delta(\mathbf{u}-\bar{\mathbf{u}}_n)\delta(\mathbf{w}-\underline{\mathbf{w}}_n),\quad \varrho_n(t)\geq 0. \tag{5.10}$$

Proposition 5.2.2 *If*

$$\mu_1(t)>0,\ \forall\, t\in[0,T], \tag{5.11}$$

$$\int_0^t \kappa_1(z-\tau)dz\geq 0,\ \forall\, t\in[0,\tau],\quad \int_0^t \kappa_1(z-\tau)dz<0,\ \forall\, t\in(\tau,T] \tag{5.12}$$

and there exist $\{\overline{\mathbf{u}}_n\}_{n=1}^N,\{\underline{\mathbf{u}}_n\}_{n=1}^N\in U$, $\{\underline{\mathbf{w}}_n\}_{n=1}^N\in W$ *such that*

$$\min_{\mathbf{u}\in U}\kappa_2(\mathbf{u})=\kappa_2(\underline{\mathbf{u}}_n),\quad \max_{\mathbf{u}\in U}\kappa_2(\mathbf{u})=\kappa_2(\overline{\mathbf{u}}_n),\quad \min_{\mathbf{w}\in W}\mu_2(\mathbf{w})=\mu_2(\underline{\mathbf{w}}_n), \tag{5.13}$$

then the measure $\hat{f}$ *can be written as follows:*

$$\hat{f}(t,\mathbf{u},\mathbf{w})=\sum_{n=1}^N \varrho_n(t)\delta(\mathbf{u}-\overline{\mathbf{u}}_n)\delta(\mathbf{w}-\underline{\mathbf{w}}_n),\quad \varrho_n(t)\geq 0,\quad \textit{for } 0<t\leq\tau, \tag{5.14}$$

$$\hat{f}(t,\mathbf{u},\mathbf{w})=\sum_{n=1}^N \varrho_n(t)\delta(\mathbf{u}-\underline{\mathbf{u}}_n)\delta(\mathbf{w}-\underline{\mathbf{w}}_n),\quad \varrho_n(t)\geq 0,\quad \textit{for } \tau<t\leq T. \tag{5.15}$$

Analytical results are illustrated by means of numerical computations performed in MATLAB making use of an implicit-explicit finite difference scheme with 200 points on the square $[-0.5,1.5]\times[-0.5,1.5]$. Interval $[0,T]$ is selected as time domain, where T is an integer multiple of the unit time $dt=0.005$. Simulations are developed assuming, alternatively,

$$f^0(u,w)=1, \tag{5.16}$$

and

$$\begin{aligned}\kappa_1(t)=\mu_1(t)=1,\ \forall\, t\in[0,T], &\qquad \kappa_2(u)=\frac{1}{1+u^2},\\ \mu_2(w)=1+w^2, &\qquad \kappa_3=\mu_3=0,\end{aligned} \tag{5.17}$$

or

$$f^0(u,w)=e^{-\frac{(u-0.5)^2}{0.1}-\frac{(w-0.5)^2}{0.1}}, \tag{5.18}$$

and

$$\mu_1(t)=0.005,\ \forall t\in[0,T],\quad \mu_2(w)=1+(w-0.5)^2,\quad \mu_3=0,\kappa_3=4, \tag{5.19}$$

$$\kappa_1(t-\tau)=10(\tau-t),\ \tau=1 \tag{5.20}$$

$$\kappa_2(u):=\begin{cases}1-u^2(1-u)^2, & \text{if } 0\leq u\leq 1,\\ 1-\min(0.06,u^2(1-u)^2), & \text{otherwise.}\end{cases}$$

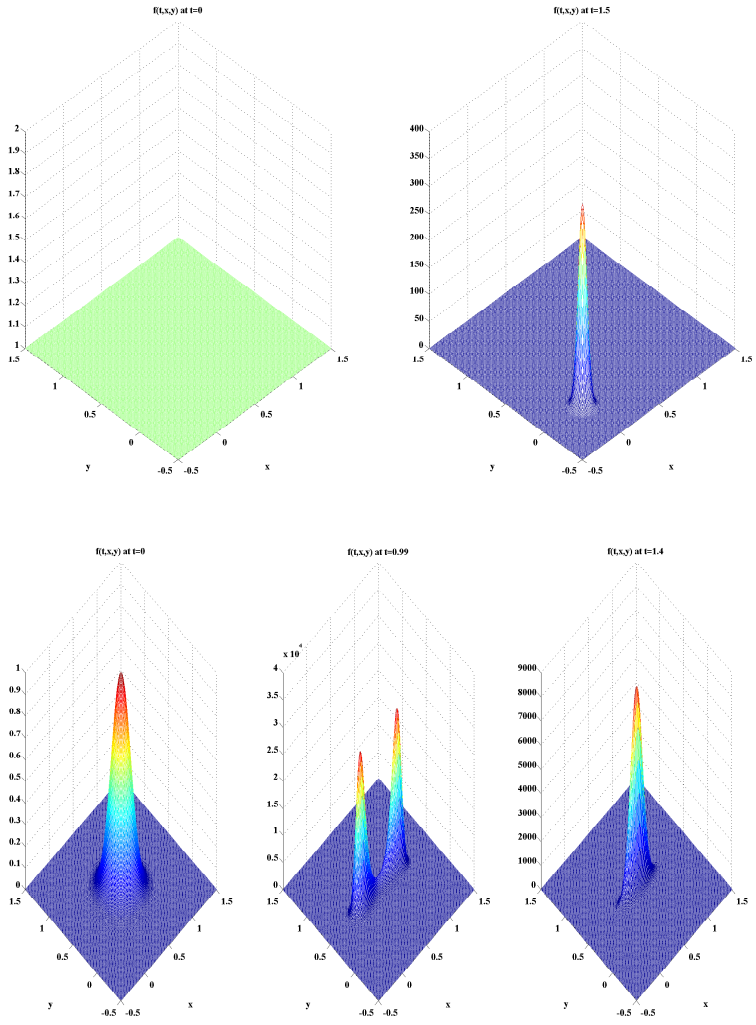

Figure 5.1: **Top panel.** Dynamics of $f(t,u,w)$, in the limit $\varepsilon \to 0$, under the assumptions of Proposition 5.2.1 with (5.17) and initial conditions (5.16). Plot of $f(t,u,w)$ for $t=0$ is on the left and for $t=T=4$ on the right. **Bottom panel.** Dynamics of $f(t,u,w)$, in the limit $\varepsilon \to 0$, under the assumptions of Proposition 5.2.2 with (5.19)-(5.21) and initial conditions (5.18). Plot of $f(t,u,w)$ for $t=0$ is on the left, for $t=0.99<\tau$ in the centre and for $t=T=1.4$ on the right.

Part IV

Models for Multicellular Systems

Introduction

The principles for successful cancer therapy
might lie not in the magic bullets of microbiology
but in the evolutionary dynamics of applied ecology
R. Gateny, A Change of Strategy in the War on Cancer

This part presents some models for the dynamics of multicellular systems. Apart from the ones introduced in Chapter 6 and Chapter 12, all these models rely on a hybrid structured-unstructured population formalism. The focus is on tumor cell dynamics, cancer-therapies and cancer-immune competition as well as immune system diseases. In more detail:

- Chapter 6 deals with an unstructured population model for the cell dynamics inside colorectal crypts, which describes cancer progression as well as the generation, through successive mutations, of multiple sub-populations of cells at different progression stages.

- Chapter 7 introduces a mathematical model for the dynamics of malignant hepatocytes under the effects of cytotoxic and targeted therapeutic agents. This model is aimed at enlightening the causes for emerging phenomena commonly observed in cancer progression, in general, and hepatocellular carcinoma, in particular.

- Chapter 8 presents a model for the dynamics of cancer hepatocytes expressing epithelial and mesenchymal phenotypes, which move via chemotaxis, proliferate and interact among themselves. The model is aimed at mimicking, at least qualitatively, some collective behaviors experimentally observed in cancer hepatocyte monolayers.

- Chapter 9 deals with the derivation, by formal asymptotic methods, of macroscopic equations for a space-velocity-structured equations describing the dynamics of epithelial and mesenchymal cells. The resulting macroscopic equations are able to reproduce biologically consistent scenarios.

- Chapter 10 presents a model for immune response against cancer, which reproduces evolutionary scenarios related to the iterative selection exerted by the immune system over cancer cells, including recognition, learning and memory aspects of the immune response.

- Chapter 11 describes a model that mimics the action of the immune system against self and non-self antigens as well as the initiation of auto-reactivity, with particular reference to the roles played by T-cells.

- Chapter 12 introduces a phenotype-structured model motivated by the theory of mutation-selection in adaptive evolution, which describes the dynamics of healthy and tumor cells under the effects of cytotoxic and cytostatic drugs.

Chapter 6

A mathematical model for progression and heterogeneity in colorectal cancer dynamics [A7,A9]

6.1 Motivations and model

A great deal of experimental evidence supports the idea that colorectal cancer is initiated by genetics mutations involving the epithelial cells that line colonic crypts (i.e. the millions of invaginations that are observed in the lining of the colon). Effective malignant mutations lead the affected cells to gain a selective advantage. Genetic alterations that do not confer a selective advantage (i.e. neutral mutations) or even alterations that confer a selective disadvantage can also take place and they may play an active part in cancer evolution [56]. However, at this stage, we do not take into account these phenomena and we analyze only the role played by successive mutations that confer increasingly selective advantages to the mutated cells. Therefore, in the following, we refer to mutated cells both as malignant cells and cancer cells.

Cells inside a crypt can be considered to be divided into three compartments [40]: stem cells, Transit-Amplifying Cells or TACs (i.e. those cells that descend from stem cells through cellular differentiation and that can be considered as semi-differentiated cells) and highly differentiated cells (i.e. those cells that result from the further differentiation of TACs and that are only able to migrate out from the crypt and to die at the end of their life-cycle). Events taking place in highly differentiated cells have a weak impact on crypt dynamics [52, 72] and these cells do not contribute to the effective population size of the crypt. Cells within each compartment are assumed to be homogeneously distributed in space. Therefore, no explicit space structures are taken into account. According

to the model that has been used by Nowak and his co-workers [52], we assume that the alteration of three genes must occur to justify the onset of colorectal cancer: the deactivation of two tumor suppressor genes (*APC* and *p-53*), which requires the neutralization of both alleles of each gene, and the alteration of one proto-oncogene (*K-ras*), which requires the alteration of only one allele of the gene (see Figure 6.1).

Focusing on the dynamics of one single crypt, we assume cells to be divided into several unstructured subpopulations. Each subpopulation is identified by and index j, which identifies the cell compartment (i.e. stem cells with $j = 1$, transit-amplifying cells with $j = 2$ and highly differentiated cells with $j = 3$) and an index $r = (1, ..., 6)$, which stands for the progression stage, as highlighted by Figure 6.1.

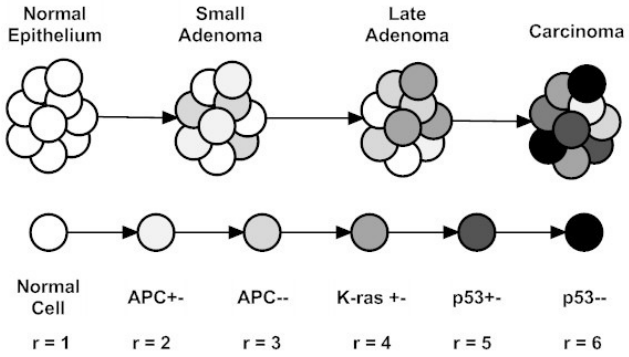

Figure 6.1: Schematic representation of colorectal cancer progression.

The state of subpopulation (j, r) is characterized by function

$$n_j^r = n_j^r(t) : [0, T] \to \mathbb{R}^+,$$

where the time variable t is normalized with respect to the life-cycle duration of the cells in subpopulation $(1, 1)$ (i.e. the life-cycle duration of normal stem cells).

The evolution of the system is ruled by the initial value problem defined by linking the following non-linear ODEs to suitable initial conditions:

$$\begin{cases} d_t n_1^1(t) &= (\gamma_1 - \beta_2^S - \beta_3^S) n_1^1(t) - \mu n_1^1(t) n_1^2(t) \\ \\ d_t n_1^q(t) &= (\gamma_q - \beta_2^S - \beta_3^S) n_1^q(t) + \beta_3^S n_1^{q-1}(t) + \\ &- n_1^q(t)(\mu n_1^{q+1}(t) + \mu^* n_1^q(t)) \\ \\ d_t n_1^R(t) &= (\gamma_R - \beta_2^S) n_1^R(t) + \beta_3^S n_1^{R-1}(t) - \mu^* n_1^R(t) n_1^R(t) \end{cases} \tag{6.1}$$

$$\begin{cases} d_t n_2^1(t) &= \beta_2^S n_1^1(t) - (\beta_2^T + \beta_3^T) n_2^1(t) - \mu n_2^1(t) n_2^2(t) \\ \\ d_t n_2^q(t) &= (\gamma_q - \beta_2^T - \beta_3^T) n_2^q(t) + \beta_2^S n_1^q(t) + \beta_3^T n_2^{q-1}(t) + \\ &- n_2^q(t)(\mu n_2^{q+1}(t) + \mu^* n_2^q(t)) \\ \\ d_t n_2^R(t) &= (\gamma_R - \beta_2^T) n_2^R(t) + \beta_2^S n_1^R(t) + \beta_3^T n_2^{R-1}(t) - \mu^* n_2^R(t) n_2^R(t) \end{cases} \tag{6.2}$$

$$\begin{cases} d_t n_3^1(t) &= \beta_2^T n_2^1(t) - \zeta n_3^1(t) \\ \\ d_t n_3^q(t) &= \beta_2^T n_2^q(t) - \zeta n_3^q(t) \\ \\ d_t n_3^R(t) &= \beta_2^T n_2^R(t) - \zeta n_3^R(t). \end{cases} \tag{6.3}$$

In the above equations $1 < q < R$, where $R \in [2; 6]$ stands for the last progression stage that can be reached by the cells during the considered time interval. For instance, the dynamics of cells, when different numbers of the mutations under consideration occur, can be described by varying the value of R (e.g. if $R = 6$, all the mutations are assumed to occur). All the parameters of the model are non-negative real numbers.

These equations should be linked to the following initial conditions in order to define a biologically consistent initial value problem:

$$\begin{cases} n_j^r(0) = n_1^0 & \text{if } r = 1 \text{ and } j = 1 \\ n_j^r(0) = n_2^0 & \text{if } r = 1 \text{ and } j = 2 \\ n_j^r(0) = n_3^0 & \text{if } r = 1 \text{ and } j = 3 \\ n_j^r(0) = 0 & \text{otherwise,} \end{cases} \tag{6.4}$$

where n_1^0, n_2^0 and n_3^0 are positive constant values. Initial conditions (6.4) mean that the system is assumed to be in healthy equilibrium at $t = 0$ (i.e. only normal cells are found inside the system) and carcinogenesis occurs at $t > 0$.

6.2 Main results

Well-posedness of the mathematical problem that is defined by linking Eqs. (6.1)-(6.3) to initial conditions in the form of (6.4) can be proved by usual Cauchy-Lipschitz theory. On the other hand, qualitative analysis and simulations can be developed with the exploratory aim of stressing the emergent phenomena that can appear within the complex system under consideration. In particular, we aimed at studying how proliferaton and mutations, that occur among cells at different differentiation levels, can affect carcinogenesis, with particular reference to progression and heterogeneity aspects.

Some mathematical models are defined, with the objectives above listed, through Eqs. (6.1)-(6.3), for low values of R. These models, which ensure both biological consistency along with analytical tractability, are linked to suitable initial conditions and the asymptotic behavior of the solutions is analyzed by means of standard methods of the dynamical systems theory.

Proposition 6.2.1 *Consider the mathematical problem that is defined by linking Eqs. (6.1), with $R = 3$ and $\gamma_1 < \beta_2^S + \beta_3^S$, to some initial conditions in the form of (6.4). If $\gamma_2 \leq \beta_2^S$ and $\gamma_3 \leq \beta_2^S$, $\hat{n}^{nul} = (0,0,0)$ is the only stable non-negative equilibrium point, while if $\gamma_2 > \beta_2^S$ and $\gamma_3 > \beta_2^S$, the equilibrium point $\hat{n}^{nul}$ becomes unstable and two additional non-negative equilibrium points occur, which are componentwise defined as:*

$$\hat{n}^{hom} = (\hat{n}_1^{1hom}, \hat{n}_1^{2hom}, \hat{n}_1^{3hom}) = (0, 0, \frac{\gamma_3 - \beta_2^S}{\mu^*}), \tag{6.5}$$

$$\hat{n}^{het} = (\hat{n}_1^{1het}, \hat{n}_1^{2het}, \hat{n}_1^{3het}) = (0, \frac{\gamma_2 - \beta_2^S - \beta_3^S}{\mu^*} - \frac{\mu}{\mu^*}\hat{n}_1^{3het}, \bar{n}_1^{3het}), \tag{6.6}$$

where

$$\hat{n}_1^{3het} = \frac{(\gamma_3 - \beta_2^S - \frac{\mu}{\mu^*}\beta_3^S) + \sqrt{(\gamma_3 - \beta_2^S - \frac{\mu}{\mu^*}\beta_3^S)^2 + 4\beta_3^S(\gamma_2 - \beta_2^S - \beta_3^S)}}{2\mu^*}.$$

Let us define $M = \dfrac{\gamma_2 - \beta_2^S - \beta_3^S}{\gamma_3 - \beta_2^S}$. If $\gamma_2 > \beta_2^S$, $\gamma_3 > \beta_2^S$ and $\beta_3^S \geq \gamma_2 - \beta_2^S$, equilibrium point $\hat{n}^{hom}$ is stable for every value of $0 < \mu, \mu^* < 1$, while equilibrium point $\hat{n}^{het}$ is unstable. On the other hand, if $\gamma_3 > \beta_2^S$ and $\beta_3^S < \gamma_2 - \beta_2^S$, equilibrium configuration $\hat{n}^{hom}$ is stable if $\mu \geq M\mu^*$, while equilibrium configuration $\hat{n}^{het}$ is stable if $\mu < M\mu^*$.

Superscripts *hom* and *het* stand for *homogeneous* and *heterogeneous*, respectively. In fact, $\hat{n}^{hom}$ identifies an homogeneous equilibrium configuration (i.e. only one component of $\hat{n}^{hom}$ is different from zero), while $\hat{n}^{het}$ defines an heterogeneous configuration (i.e. more than one component of $\hat{n}^{het}$ is greater than zero).

Remark 6.3 *For every value of β_3^S, if $\gamma_2 \leq \beta_2^S$ and $\gamma_3 \leq \beta_2^S$ then $\hat{n}^{nul}$ is the only non-negative stable equilibrium point. On the other hand, if $\gamma_2 > \beta_2^S$, $\gamma_3 > \beta_2^S$ and $\beta_3^S \geq \gamma_2 - \beta_2^S$, $\hat{n}^{hom}$ is the only stable configuration.*

Analytical results are extended by means of numerical simulations performed in MATLAB making use of a standard finite difference scheme. Interval $[0, T]$ is selected as time domain, where $T = 10000$ is an integer multiple of the unit time $dt = 0.01$.

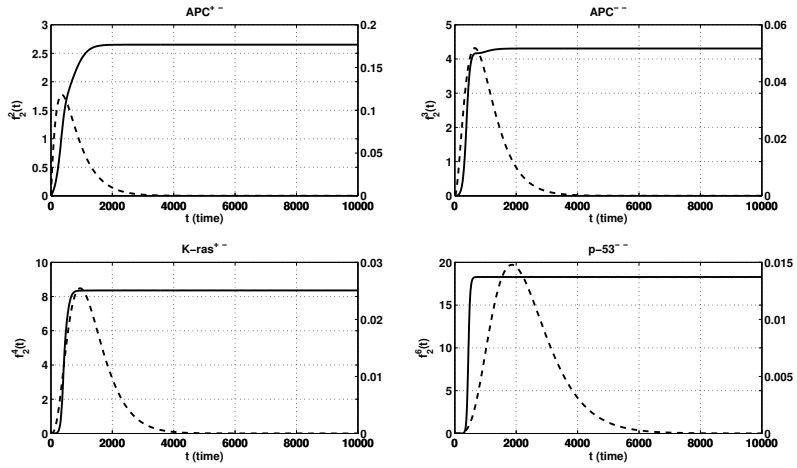

Figure 6.2: Dynamics of $n_2^r(t)$ for $r = (2, 3, 4, 6)$, i.e. time dynamics of the densities of TACs that are found inside a crypt at progression stage r. The simulations are developed allowing mutations to involve both the stem cells and the TACs. The dashed lines are referred to the y-axis on the right and they are related to numerical results that are obtained with the proliferation rate $\gamma_r < \beta_2^S$. The solid lines are referred to the y-axis on the left and they are related to the simulations that are developed with $\gamma_r > \beta_2^S$. If $\gamma_r < \beta_2^S$, the number of cancer cells at each progression stage $r \geq 2$ tends to zero in time, for every value of β_3^S. On the other hand, if $\gamma_r > \beta_2^S$ the number of cancer cells can reach a finite value in time. Therefore cancer development seems to require an increase in the proliferation rate rather than in the mutation rate of the malignant cells.

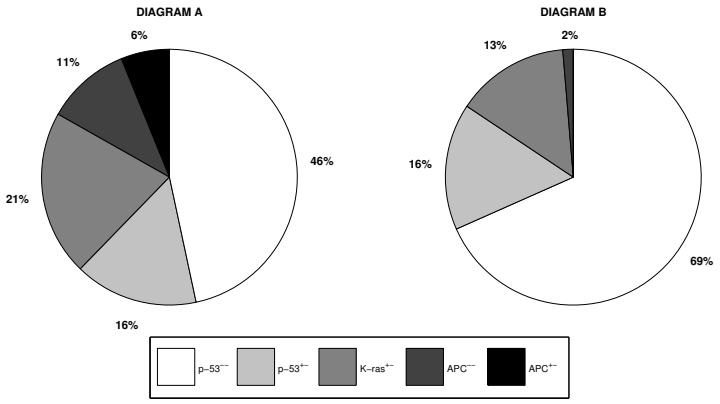

Figure 6.3: Percentage distribution of TACs over progression stages $r = (2, ..., 6)$ for two different values of the mutation rate, at time $t = 5000$. The simulations are developed allowing the mutations to involve both the stem cells and the TACs. The grayscale refers to progression stage r and ranges from white ($r = 6$) to black ($r = 2$). The two diagrams refer to the same value of γ_r, which is chosen so that cancer growth can occur. DIAGRAM A is obtained by setting the mutation rate equal to a lower value with respect to the one considered in the case of DIAGRAM B. A higher mutation rate causes the tumor to progress quickly; as a result, most of the cells are found at the same progression stage at the end of the selected time interval. On the other hand, a lower mutation rate leads to a slow tumor progression; therefore, cells are spread over different progression stages at the end of the same time interval. Hence, a low mutation rate provides the basis for intra-tumor heterogeneity.

Chapter 7

A mathematical model for the dynamics of cancer hepatocytes under therapeutic actions [A6,A8]

7.1 Motivations and model

Among tumor pathologies, HepatoCellular Carcinoma (HCC) has a poor prognosis and represents the third most cause of death from cancer worldwide, due to diagnosis at advanced stages and lack of effective therapy options [30]. The evolution of epithelial cells into mesenchymal cells, the so-called Epithelial to Mesenchymal Transition (EMT) [66, 67], has been postulated to be a crucial event in HCC progression and recurrence [69]. A human model for the progression of hepatocellular carcinoma through EMT has been proposed in [69] and it has been used to test the efficacy against cancer cells of two classes of therapeutic agents: Targeted Therapeutic Agents (TTAs), which can be addressed to act over cells that express some given genetic and epigenetic alterations, and Cytotoxic Agents (CAs), which work by leading cells to die almost independently from their genotype or phenotype.

Taking advantage of such human model, in this paper we present a mathematical model for the *in vitro* dynamics of malignant hepatocytes under the effects of anti-cancer therapies, which is aimed at enlightening the causes for emerging phenomena that can be observed in cancer progression, in general, and hepatocellular carcinoma, in particular. The model consists of a set of integrodifferential equations describing the dynamics of tumor cells under the effects of mutation, competition for space and resources, interactions with cytokines regulating cell proliferation as well as the action of cytotoxic drugs and targeted therapeutic agents.

The reference system is defined by a well-mixed sample of epithelial and mesenchymal cancer cells of the liver, which are considered as divided into two structured subpopulations labeled, respectively, by indexes $i = 1$ and $i = 2$. On the other hand, cytokines responsible for cell proliferation and produced by cancer cells are supposed to be grouped into an additional unstructured subpopulation, identified by index $i = 3$. Subpopulation $i = 1$ and subpopulation $i = 2$ are structured by a continuous variable $s \in S := [0, 1]$ that represents the genotypic-phenotypic profile of the cells. Since mutations are assumed to be small and to occur on a longer time scale than proliferation, a parameter ε is introduced to model the ratio between these time scales as well as the average size of mutations.

The states of the subpopulations are characterized by functions

$$f_1 = f_1(t, s) : \mathbb{R}^+ \times S \to \mathbb{R}^+, \qquad f_2 = f_2(t, s) : \mathbb{R}^+ \times S \to \mathbb{R}^+,$$

and

$$n_3 = n_3(t) : \mathbb{R}^+ \to \mathbb{R}^+,$$

where the time variable t is normalized with respect to the duration of the average life-cycle of cancer cells. At any fixed time t, the quantity $f_i(t, s)\, ds$ stands for the number of cells in subpopulation $i = 1, 2$ whose microscopic state belongs to the volume element ds centered at s, normalized with respect to the total number of particles (i.e. cells and cytokines) inside the system at time $t = 0$. Thus, cell densities at time t can be computed as:

$$\varrho_i(t) = \int_S f_i(t, s) ds, \qquad i = 1, 2. \tag{7.1}$$

Cytotoxic drugs and targeted therapeutic agents are seen as particles belonging to two additional subpopulations labeled, respectively, by indexes $j = 1$ and $j = 2$. Subpopulation $j = 1$ is assumed to be unstructured, while subpopulation $j = 2$ is structured by the continuous variable s, in this case related to the genotypic-phenotypic profile of the cells that can be mainly recognized and attacked by the curing agents. The states of these additional subpopulations are described by functions:

$$g_1 : \mathbb{R}^+ \to \mathbb{R}^+, \quad g_1 \in L^1([0, \infty)) \cap L^\infty([0, \infty)), \quad \|g_1(\cdot)\|_{L^\infty([0,\infty))} \leq 1,$$

$$g_2(t, s) = c_2(t) b_2(s), \quad b_2 : S \to \mathbb{R}^+, \quad b_2 \in L^1(S), \quad \|b_2(\cdot)\|_{L^1(S)} = 1,$$

$$c_2 : \mathbb{R}^+ \to \mathbb{R}^+, \quad c_2 \in L^1([0, \infty)) \cap L^\infty([0, \infty)), \quad \|c_2(\cdot)\|_{L^\infty([0,\infty))} \leq 1. \tag{7.2}$$

We describe the dynamics of the system through the following Cauchy Problem

$$\begin{cases} \partial_t \mathbf{h}(t, s) = \mathcal{H}[\mathbf{h}](t, s), \quad (t, s) \in (0, T] \times S \\ \\ \mathbf{h}(0, s) = \mathbf{h}^0(s), \end{cases} \tag{7.3}$$

where

$$\mathbf{h}(t,s) = (f_1(t,s), f_2(t,s), n_3(t)), \quad \mathbf{h}^0(s) = (f_1^0(s), f_2^0(s), n_3^0),$$

with

$$f_1^0(s), f_2^0(s) \in L^1(S), \quad f_1^0(s), f_2^0(s) > 0 \text{ a.e. on } S, \quad n_3^0 \in \mathbb{R}^+,$$

while $\mathcal{H}$ is componentwise defined by the set of integro-differential equations given hereafter:

$$\begin{aligned}
\partial_t f_i(t,s) &= \underbrace{\sum_{k=1}^{2} \int_S \mathcal{A}_k^i(s_*, s; \varepsilon) f_k(t, s_*) du_* - f_i(t,s)}_{\text{EMT, mutations and renewal}} + \underbrace{\kappa(s) n_3(t) f_i(t,s)}_{\text{cell proliferation}} \\
&- \underbrace{\mu(s) f_i(t,s)(\varrho_1(t) + \varrho_2(t))}_{\text{cell-cell competition}} - \underbrace{\mu^T g_1(t) f_i(t,s)}_{\text{destruction due to CAs}} \\
&- \underbrace{\mu^T f_i(t,s) \int_S e^{-\theta^T (s^* - s)^2} g_2(t, s^*) ds^*}_{\text{destruction due to TTAs}} \qquad (7.4) \\
d_t n_3(t) &= \underbrace{\mu^K (\varrho_1(t) + \varrho_2(t))}_{\text{secretion of cytokines}} \underbrace{- n_3(t) \sum_{k=1}^{2} \int_S \kappa(s^*) f_k(t, s^*) ds^*}_{\text{consumption of cytokines}},
\end{aligned}$$

where:

$$\mathcal{A}_k^i(s_*, s; \varepsilon) = \begin{cases} (1-\gamma_1) M_k(s - s_*; \varepsilon), & \text{if } \ i = k = 1 \\ \gamma_1 M_k(s - s_*; \varepsilon), & \text{if } i = 2 \text{ and } k = 1 \\ (1-\gamma_2) M_k(s - s_*; \varepsilon), & \text{if } \ i = k = 2 \\ \gamma_2 M_k(s - s_*; \varepsilon), & \text{if } i = 1 \text{ and } k = 2, \end{cases} \qquad (7.5)$$

$$M_k(s - s_*; \varepsilon) := \begin{cases} \alpha_k \delta(s - (s_* \pm \varepsilon)) + (1 - 2\alpha_k)\delta(s - s_*), & \text{if } \varepsilon < s < 1 - \varepsilon \\ \alpha_k \delta(s - (s_* - \varepsilon)) + (1 - \alpha_k)\delta(s - s_*), & \text{if } 0 \le s \le \varepsilon \\ \alpha_k \delta(s - (s_* + \varepsilon)) + (1 - \alpha_k)\delta(s - s_*), & \text{if } 1 - \varepsilon \le s \le 1, \end{cases}$$

where δ is the Dirac's delta distribution,

$$\kappa : S \to \mathbb{R}^+, \quad \kappa \in W^{2,\infty}(S), \quad \inf_s \kappa(s) > 0. \qquad (7.6)$$

and

$$\mu : S \to \mathbb{R}^+, \quad \mu \in W^{2,\infty}(S), \quad \inf_s \mu(s) > 0. \qquad (7.7)$$

The above definition for $M_k(s - s_*; \varepsilon)$ translates into mathematical terms the idea that mutations are small, i.e. only small variations in the phenotypic trait can occur from parent to offspring.

7.2 Main results

Standard fixed point arguments can be used to show that Cauchy Problem (7.3) is well-posed, in the sense of Hadamard, and admits a unique global in time solution.

Then, we turn to the study of the asymptotic behavior, in the limit $\varepsilon \to 0$, of the solution to the Cauchy Problem (7.3). In particular, after introducing the below notations

$$\mathbf{f}_\varepsilon(t,s) = \mathbf{f}\left(\frac{t}{\varepsilon}, s\right),$$

$$f^0(s) = f_1^0(s) + f_2^0(s), \quad f_\varepsilon(t,s) = f_{1\varepsilon}(t,s) + f_{2\varepsilon}(t,s),$$

$$\begin{aligned} R_\varepsilon(t,s) &= \int_0^t \kappa(s) n_{3\varepsilon}(z) - \mu(s) \int_S f_\varepsilon(z,s^*) ds^* - \mu^T g_1(z) dz \\ &- \int_0^t \mu^T \int_S e^{-\theta^T (s^*-s)^2} g_2(z,s^*) ds^* dz, \end{aligned}$$

with $i = 1, 2$, we show how, under some additional assumptions, an approach similar to the one proposed in [25] can be used to study the asymptotic behavior of the solution of Eqs. (7.3), which include the model studied in [25] as a particular case. In fact, Eqs. (7.3) include, as additional elements, mutation phenomena and interactions involving both structured and unstructured populations. Such a result is established by the following:

Theorem 7.2.1 *There exist a subsequence of f_ε, denoted again as f_ε, and a subsequence of R_ε, denoted again as R_ε, such that:*

i) Establishing convergence.

$$f_\varepsilon \rightharpoonup \hat{f} \text{ on } w^* - L^\infty((0,T), M^1(S)), \quad \text{as } \varepsilon \to 0,$$

$$R_\varepsilon \to R \text{ uniformly in } [0,T] \times S, \quad \text{as } \varepsilon \to 0,$$

where $\hat{f} \in L^\infty((0,T), M^1(S))$,

$$R(t,s) = \int_0^t P(z,s) dz \in W^{2,\infty}((0,T) \times S) \tag{7.8}$$

and

$$\max_{s \in S} R(t,s) = 0, \qquad \forall\, t \in [0,T].$$

ii) Characterizing the support of the limit $\hat{f}$.
Assume

$$\mu^T < n_3^0 < \frac{\mu^K \|f^0(\cdot)\|_{L^1(S)}}{\int_S \kappa(s^*) f^0(s^*) ds^*}, \quad \inf_s \kappa(s) > 2\varepsilon \quad \|\kappa(\cdot)\|_{L^\infty(S)} = \kappa^C < 1, \tag{7.9}$$

then

$$supp(\hat{f}(t,\cdot)) \neq \emptyset, \quad supp(\hat{f}(t,\cdot)) \subset R(t,\cdot)^{-1}(0), \quad \textit{for a.e. } t \in [0,T].$$

iii) Identifying the limit $\hat{f}$.
If the function $\kappa(s)$ has a positive maximum κ^C attained at some points $\{\hat{s}_n\}_{n=1}^N$, with $N \in \mathbb{N}$, then the measure f results as follows:

$$\hat{f}(t,s) = \sum_n \varrho_n(s)\delta(s-\hat{s}_n), \quad \varrho_n(t) \geq 0.$$

In order to illustrate and extend analytical results, we numerically solve, under different parameter settings, the Cauchy Problem (7.3). Numerical simulations are performed in MATLAB by means of a collocation method with 200 points on $[0,1]$. Interval $[0,T]$ is selected as time domain, where $T = 100$ is an integer multiple of the unit time $dt = 0.005$. In particular, we set $\varepsilon = 0.001$ (i.e. $\varepsilon \to 0$),

$$\kappa(s) := \kappa^C \, e^{-[(s-0.25)^2+(s-0.75)^2]/0.3}, \quad \kappa^C \in \mathbb{R}^+, \tag{7.10}$$

$\mu(s,s^*) = \mu_1(s)\mu_2(s^*)$ with

$$\mu_1(s) := \mu_1^C \in \mathbb{R}^+, \qquad \mu_2(s) := \mu_2^C \in \mathbb{R}^+ \tag{7.11}$$

and assume, alternatively,

$$g_1(t) = 0, \qquad c_2(t) = 0, \ \forall t \in \mathbb{R}^+, \tag{7.12}$$

or

$$g_1(t) = 0, \qquad c_2(t) := \mathbf{1}_{[50,100]}(t), \quad b_2(s) := C_2 e^{-\frac{(s-0.25)^2}{0.01}}, \tag{7.13}$$

where $\mathbf{1}$ is the indicator function and $C_2 \in \mathbb{R}^+$ is such that

$$\int_S b_2(s) \, ds = 1.$$

Definitions (7.12) refer to the situation where therapeutic agents are not delivered, while definition (7.13) mimic a scenario where targeted therapeutic agents, inoculated in the sample at time $t = 50$, are mainly able to act against cancer cells expressing the genotypic-phenotypic profile corresponding to $s = 0.25$, while cytotoxic agents are not delivered.

Simulations are meant to:

- enlighten the role played by the biological phenomena under consideration in cancer dynamics, with particular reference to progression and heterogeneity aspects;
- verify the consistency of our model with respect to the biological conclusions drawn in [69];
- highlight some emerging behaviors related to the effects of therapeutic actions on cancer dynamics.

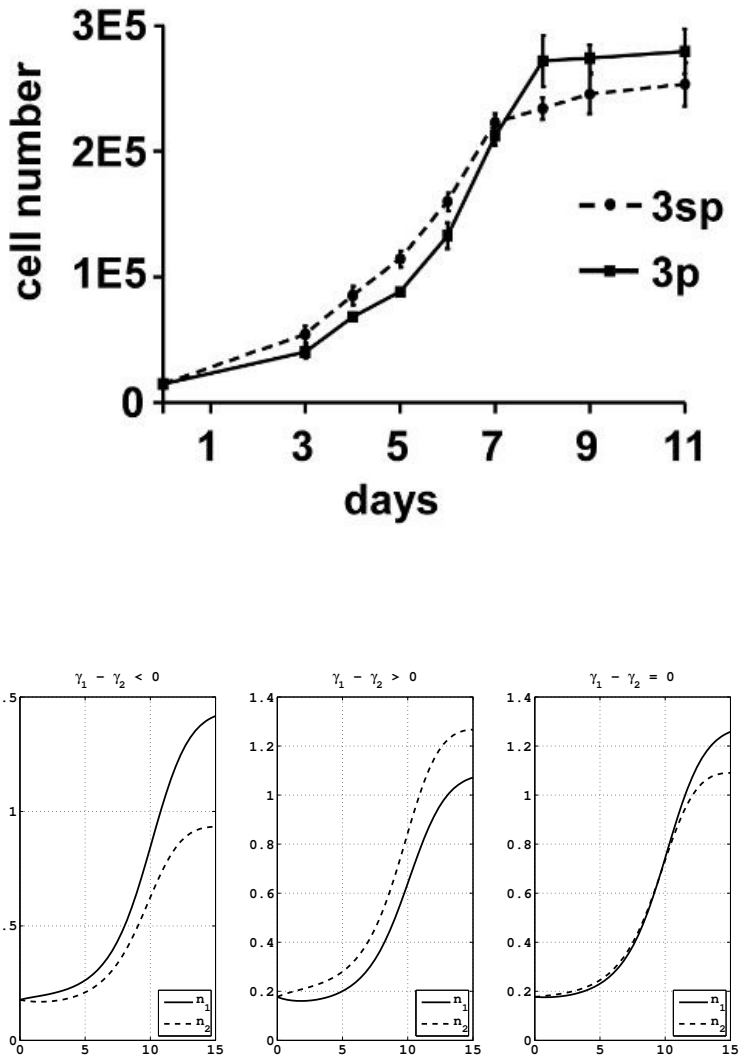

Figure 7.1: **Top panel.** Experimental trends of the number of epithelial (3p) and mesenchymal (3sp) cells (figure reproduced from [69]). **Bottom panel.** Dynamics of $\varrho_1(t)$ and $\varrho_2(t)$ for different values of $\gamma_1 - \gamma_2$ (i.e. the difference between the probabilities for direct and reverse EMT). The parameter setting under consideration ensures that, when $\gamma_1 - \gamma_2 = 0$, $\varrho_2(t)$ increases faster than $\varrho_1(t)$ for lower cell numbers, while the opposite behavior is observed for higher cell numbers.

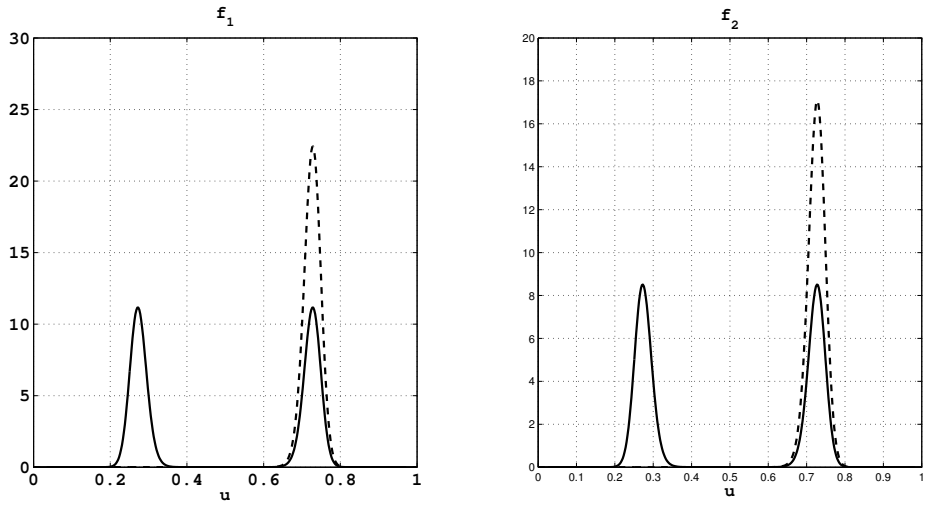

Figure 7.2: Trends of $f_1(t = 100, s)$ and $f_2(t = 100, s)$ in the limit $\varepsilon \to 0$ under conditions (7.12) (solid lines) and conditions (7.13) (dashed lines). In the first case function $f_1(t, s)$ and $f_2(t, s)$ concentrate, across time, around the points where $\kappa(s)$ (i.e. the probability for cell proliferation) attains its maximum. This result supports the idea that, in the limit of small mutations, only cells endowed with strong proliferative abilities can survive inside the sample. On the other hand, in the second case, due to the fact that $g_2(t, s)$ is mainly concentrated around point $s = 0.25$, the picks of $f_1(t, s)$ and $f_2(t, s)$ centered in $s = 0.25$ vanish over time. These results also suggest that targeted therapeutic agents can select for resistance: if environmental conditions select for strong proliferative abilities and two groups of highly proliferative clones are found inside the system, and if therapeutic actions cause the targeted extinction of one group, the clonal expansion of cells in the other group is intensified.

Chapter 8

A mathematical model for adhesion and diffusion in cancer hepatocyte monolayers [A13]

8.1 Motivations and model

Evidence is accumulating that the trans-differentiation of cancer epithelial cells of the liver into motile and invasive mesenchymal cells, the so-called Epithelial to Mesenchymal Transition (EMT) can play a crucial role in metastatic processes. In particular, EMT seems also to be involved in the formation of those fibrous capsules that are frequently observed in hepatocellular carcinoma (see Figure 8.1). This is suggested by histopathological evidence for the fact that such capsules are mainly formed by mesenchymal cells [38].

As a result, the design of a mathematical model able to mimic this kind of aggregation and diffusion behaviors may allow a deeper comprehension of some mechanisms underling the progression of hepatocellular carcinoma [34, 69, 71]. With this aim, this paper proposes a model describing the dynamics of a monolayer culture of cancer hepatocytes expressing epithelial and mesenchymal phenotypes (i.e. on account of brevity, 3p and 3sp cells, respectively), which move via chemotaxis on a flat surface, proliferate and interact among themselves. The goal of the model is to reproduce, at least qualitatively, the opposite collective behaviors expressed by these cells in co-culture: the ability of epithelial cells to adhere to one another and the tendency of mesenchymal cells to diffuse through the sample [69].

Epithelial and mesenchymal cells in motion are here grouped into two distinct subpopulations (i.e. $i = 1, 2$), structured by position $\mathbf{x} = (x, y)$ and velocity $\mathbf{v} = (v_x, v_y)$ of the cells (i.e. $(\mathbf{x}, \mathbf{v})$ is a point in the phase space). Two

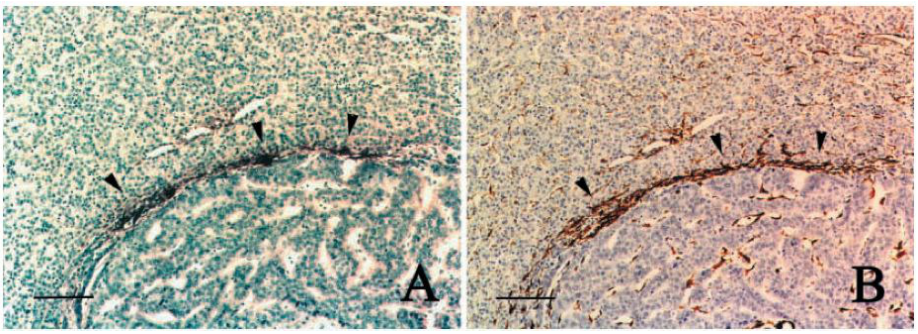

Figure 8.1: Fibrous capsules as the ones typically observed in hepatocellular carcinoma. Figure reproduced from [38].

additional subpopulations are introduced, which collect, respectively, epithelial cells stuck together due to homotypic adhesion (i.e. the attachment among identical cells) and cytokines, secreted by cancer cells, that are responsible for chemotaxis, which are labeled by index $i = 3, 4$, respectively. The space variable $\mathbf{x}$ is assumed to be normalized with respect to the average size of hepatocytes. Therefore, we allow X to coincide with the whole space $\mathbb{R}^2$ to account for the fact that the area of the dish can be much larger than the area covered by the cell monolayer. Finally, following [18], we assume V to be compact and spherically symmetric.

The states of these subpopulations are described by functions

$$f_1 = f_1(t, \mathbf{x}, \mathbf{v}) : \mathbb{R}^+ \times X \times V \to \mathbb{R}^+, \qquad f_2 = f_2(t, \mathbf{x}, \mathbf{v}) : \mathbb{R}^+ \times X \times V \to \mathbb{R}^+,$$

and

$$n_3 = n_3(t, \mathbf{x}) : \mathbb{R}^+ \times X \to \mathbb{R}^+, \qquad n_4 = n_4(t, \mathbf{x}) : \mathbb{R}^+ \times X \to \mathbb{R}^+.$$

where the time variable t is normalized with respect to the duration of the average life-cycle of cancer cells. At any fixed time t, the quantity $f_i(t, \mathbf{x}, \mathbf{v})\, d\mathbf{v}$ stands for the number of cells in $\mathbf{x}$ whose velocity belongs to the volume element $d\mathbf{v}$ centered in $\mathbf{v}$, normalized with respect to the total number of particles (i.e. cells and cytokines) inside the system at time $t = 0$. Therefore, the local densities of 3p and 3sp cells can be computed as follows:

$$\varrho_i(t, \mathbf{x}) = \int_V f_i(t, \mathbf{x}, \mathbf{v}) d\mathbf{v}, \qquad i = 1, 2. \tag{8.1}$$

On the other side, the quantities $\varrho_1(t, \mathbf{x})\, d\mathbf{x}$, $\varrho_2(t, \mathbf{x})\, d\mathbf{x}$, $n_3(t, \mathbf{x})\, d\mathbf{x}$ and $n_4(t, \mathbf{x})\, d\mathbf{x}$ represent the normalized numbers of cells and cytokines inside the volume element $d\mathbf{x}$ centered at $\mathbf{x}$. As a result, the total density of cells and the normalized size of the whole sample can be, respectively, computed as follows:

$$\varrho(t, \mathbf{x}) = \sum_{i=1}^{2} \varrho_i(t, \mathbf{x}) + n_3(t, \mathbf{x}), \qquad N(t) = \int_X \varrho(t, \mathbf{x}) + n_4(t, x)\, d\mathbf{x}, \tag{8.2}$$

where normalization implies $N(0) = 1$.

Functions $f_1(t, \mathbf{x}, \mathbf{v})$, $f_2(t, \mathbf{x}, \mathbf{v})$, $n_3(t, \mathbf{x})$ and $n_4(t, \mathbf{x})$ evolve according to the equations given hereafter, which describe the net inlet of moving epithelial and mesenchymal cells through the volume element $d\mathbf{x}\ d\mathbf{v}$ of the phase space centered in $(\mathbf{x}, \mathbf{v})$, as well as the net flux of aggregated epithelial cells and cytokines through the volume element $d\mathbf{x}$ centered in $\mathbf{x}$, due to the phenomena under consideration:

$$
\begin{aligned}
&\partial_t f_1(t,\mathbf{x},\mathbf{v}) + \mathbf{v}\cdot\nabla_{\mathbf{x}} f_1(t,\mathbf{x},\mathbf{v}) = \\
&\qquad \underbrace{\left(\frac{\alpha}{|V|} + \beta\mathbf{v}\cdot\nabla_{\mathbf{x}} n_4(t,\mathbf{x})\right)\varrho_1(t,\mathbf{x}) - \alpha f_1(t,\mathbf{x},\mathbf{v})}_{\text{random motion and velocity modification due the cytokines' gradient}} \\
+ &\qquad \underbrace{\eta\frac{(1-\gamma)}{|V|}\varrho_1(t,\mathbf{x})\varrho_1(t,\mathbf{x}) + \eta\frac{(1-\gamma)}{|V|}\varrho_1(t,\mathbf{x})n_3(t,\mathbf{x})}_{\text{velocity modifications due to cell-cell interactions and homotypic adhesion}} \\
+ &\qquad \underbrace{\frac{\eta}{|V|}\varrho_1(t,\mathbf{x})\varrho_2(t,\mathbf{x}) - \eta\varrho(t,\mathbf{x})f_1(t,\mathbf{x},\mathbf{v})}_{\text{velocity modifications due to cell-cell interactions and homotypic adhesion}} \\
+ &\underbrace{\left(\kappa - \mu\int_X \varrho(t,\mathbf{x})d\mathbf{x}\right) f_1(t,\mathbf{x},\mathbf{v})}_{\text{proliferation and competition}}
\end{aligned}
\tag{8.3}
$$

$$
\begin{aligned}
&\partial_t f_2(t,\mathbf{x},\mathbf{v}) + \mathbf{v}\cdot\nabla_{\mathbf{x}} f_2(t,\mathbf{x},\mathbf{v}) = \\
&\qquad \underbrace{\left(\frac{\alpha}{|V|} + \beta\mathbf{v}\cdot\nabla_{\mathbf{x}} n_4(t,\mathbf{x})\right)\varrho_2(t,\mathbf{x}) - \alpha f_2(t,\mathbf{x},\mathbf{v})}_{\text{random motion and velocity modification due the cytokines' gradient}} \\
+ &\qquad \underbrace{\frac{\eta}{|V|}\varrho(t,\mathbf{x})\varrho_2(t,\mathbf{x}) - \eta\varrho(t,\mathbf{x})f_2(t,\mathbf{x},\mathbf{v})}_{\text{velocity modifications due to cell-cell interactions}} \\
+ &\underbrace{\left(\kappa - \mu\int_X \varrho(t,\mathbf{x})d\mathbf{x}\right) f_2(t,\mathbf{x},\mathbf{v})}_{\text{proliferation and competition}}
\end{aligned}
\tag{8.4}
$$

$$
\begin{aligned}
\partial_t n_3(t,\mathbf{x}) \;=\; &\underbrace{\eta\gamma\left(\varrho_1(t,\mathbf{x})\varrho_1(t,\mathbf{x}) + \varrho_1(t,\mathbf{x})n_3(t,\mathbf{x})\right)}_{\text{homotypic adhesion}} \\
+ \;&\underbrace{\left(\kappa - \mu\int_X \varrho(t,\mathbf{x})d\mathbf{x}\right) n_3(t,\mathbf{x})}_{\text{proliferation and competition}}
\end{aligned}
\tag{8.5}
$$

$$\partial_t n_4(t,\mathbf{x}) = \underbrace{\nu\varrho(t,\mathbf{x}) + \Delta_{\mathbf{x}} n_4(t,\mathbf{x})}_{\text{secretion and diffusion}} - \underbrace{\lambda n_4(t,\mathbf{x})}_{\text{decay}}. \tag{8.6}$$

All the above introduced parameters, are non-negative real numbers. The collective behavior of cells and cytokines can be studied by analyzing the dynamics of the solutions to the Cauchy Problem defined by endowing Eqs.(8.3)-(8.6) with suitable initial conditions.

8.2 Main results

Taking advantage of the analytical methods presented in [18, 37], we establish a weak global existence result for a biologically consistent Cauchy Problem defined by endowing Eqs.(8.3)-(8.6) to the initial conditions given hereafter:

$$f_i(0,\mathbf{x},\mathbf{v}) = f_i^0(\mathbf{x},\mathbf{v}) \geq 0 \text{ on } \mathbb{R}^2 \times V, \quad f_i^0, \nabla_{\mathbf{x}} f_i^0 \in L^1 \cap L^\infty(\mathbb{R}^2 \times V), \tag{8.7}$$

$$n_3(0,\mathbf{x}) = n_3^0(\mathbf{x}) \geq 0, \ \forall \mathbf{x} \in \mathbb{R}^2, \quad n_3^0, \nabla_{\mathbf{x}} n_3^0 \in L^1 \cap L^\infty(\mathbb{R}^2), \tag{8.8}$$

$$\varrho(0,\mathbf{x}) = \varrho^0(\mathbf{x}), \quad \|\varrho^0\|_{L^1(\mathbb{R}^2)} < \frac{\kappa}{\mu}, \tag{8.9}$$

$$n_4(0,\mathbf{x}) = 0, \ \forall \mathbf{x} \in \mathbb{R}^2. \tag{8.10}$$

Theorem 8.2.1 *Let us assume, without loss of generality, $\nu = \alpha = \beta = \eta = 1$ and $X = \mathbb{R}^2$. Then, the Cauchy Problem defined by Eqs.(8.3)-(8.6) endowed with initial conditions (8.7)-(8.10) has a global weak solution componentwise defined by*

$$f_i \in L^\infty_{loc}((0,\infty); L^1 \cap L^\infty(\mathbb{R}^2 \times V)), \quad \nabla_{\mathbf{x}} f_i \in L^\infty_{loc}((0,\infty); L^1 \cap L^\infty(\mathbb{R}^2 \times V)),$$

for $i = 1, 2$,

$$n_3 \in L^\infty_{loc}((0,\infty); L^1 \cap L^\infty(\mathbb{R}^2)), \quad \nabla_{\mathbf{x}} n_3 \in L^\infty_{loc}((0,\infty); L^1 \cap L^\infty(\mathbb{R}^2)),$$

and

$$n_4 \in L^\infty_{loc}((0,\infty); L^p(\mathbb{R}^2)), \quad \nabla_{\mathbf{x}} n_4 \in L^\infty_{loc}((0,\infty); L^p(\mathbb{R}^2)),$$

for any $1 \leq p \leq \infty$.

Then, we perform numerical simulations meant to reproduce, at least qualitatively, aggregation and dispersion phenomena usually observed in cell monolayers composed of epithelial and mesenchymal cancer hepatocytes. With this aim, we approximate cellular velocities in polar coordinates as follows:

$$\mathbf{v}(t) = \begin{pmatrix} v_x \\ v_y \end{pmatrix} = v_0 \begin{pmatrix} \cos\theta(t) \\ \sin\theta(t) \end{pmatrix}, \tag{8.11}$$

where, on account of simplicity, we assume that cells move at constant speed normalized to the unity, i.e. $v_0 = 1$, so that cell distributions can be computed tracking space and velocity angles only.

Simulations are performed in MATLAB. Making reference to the numerical method, spatial and angular terms are discretized considering a spatial grid of 56×56 nodes, with periodic boundary conditions, and 32 velocity angle points. A time splitting scheme is adopted to treat the advection, source and conservative terms, i.e the right hand sides of the model (8.3)-(8.6). The advection term representing cell movement is approximated in conservative form using a flux-limiting scheme. Integral terms are computed using a trapezioidal scheme. Time integration of the resulting large system of time dependent ODEs is performed using a $4th$ order Runge Kutta scheme. The reaction-diffusion equation for the cytokines is approximated by a classical second order finite difference scheme. Simulations are performed until time $T = 80$, the square $[-15, 15] \times [-15, 15]$ and the interval $[0, 360]$ are selected, respectively, as x-domain and θ-domain.

We numerically solve the mathematical problem defined by Eqs. (8.3)-(8.6) coupled to the following initial conditions:

$$f_{1,2}(t = 0, x, y, \theta(t = 0)) = 10e^{-(x^2+y^2)}, \quad n_{3,4}(t = 0, x, y) = 0. \tag{8.12}$$

The first ones mimic a sample where epithelial and mesenchymal cancer hepatocytes in motion are mainly concentrated in the center of the domain and their velocities are homogeneously distributed over all directions at beginning of observations. The second ones reproduce a situation where neither epithelial cancer cells stuck together due to homotypic adhesion nor citokynes are initially found within the sample.

All the parameters are set equal to suitable non-zero values selected with exploratory aim:

- The average rates of velocity changes due to random motion and chemotaxis are set, respectively, as $\alpha = 0.001$ and $\beta = 0.1$.

- The aggregation rate of epithelial cells through homotypic adhesion is set as $\gamma = 0.1$.

- The average proliferation rate, net of apoptosis, is set as $k = 0.008$ and the parameter related to apotosis due to competition for resources as $\mu = 0.003$.

- Parameters related to cytokines responsible for cell movement are set as $\lambda = 0.1$ and $\nu = 0.1$.

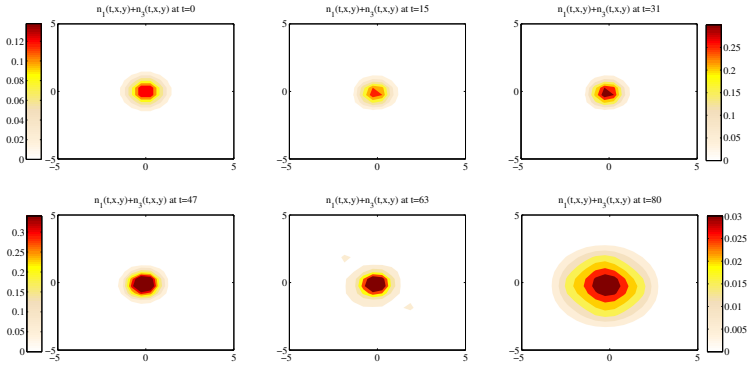

Figure 8.2: Profile of $\varrho_1(t,x,y) + n_3(t,x,y)$ at final time $T = 80$. Epithelial hepatocytes tend to stay adhered one to the other through homotypic adhesion.

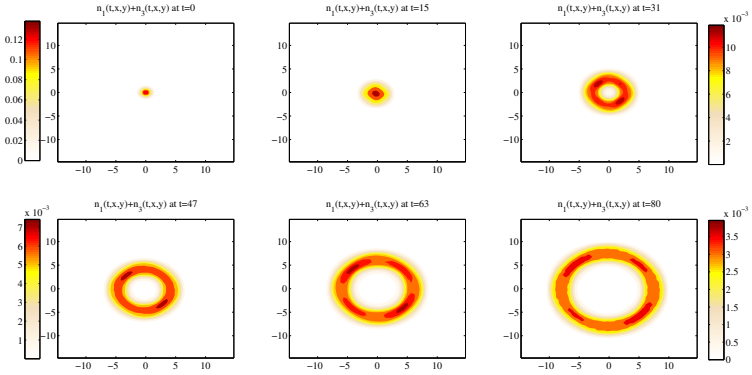

Figure 8.3: Profile of $\varrho_2(t,x,y)$ at final time $T = 80$. Mesenchymal hepatocytes fail to aggregate and tend to form a propagating rim of cells. This emerging behavior is consistent with the histopathological evidence suggesting that the capsules frequently observed in hepatocellular carcinoma are mainly composed of mesenchymal cells.

Chapter 9

Drift-diffusion limit of a model for the dynamics of epithelial and mesenchymal cell monolayers [A14]

9.1 Motivations and model

The term epithelial to mesenchymal transition refers to the process leading non-motile epithelial cells, which tend to stay collectively embedded through cell-cell junctions (i.e. the so-called homotypic adhesion), to convert into individual and motile mesenchymal cells, which tend to avoid aggregation and diffuse following cytokine gradients [72].

This paper is devoted to prove the diffusive scaling limit for a model that describes the dynamics of a monolayer culture of epithelial and mesenchymal cells, which move via chemotaxis on a flat surface, proliferate and interact among themselves. With this aim, we introduce a small parameter ε, standing for the ratio between the mean free paths of random motion and chemotactic reorientation, and we perform a diffusive scaling of time and position. Furthermore, we assume chemotaxis along the cytokines' gradient and motion reorientations due to cellular interactions to be perturbations of order ε with respect to random motion. Finally, we consider interactions leading to homotypic adhesion to be a further perturbation of order ε with respect to those interactions that lead to velocity reorientation [72].

The limit $\varepsilon \to 0$ is formally carried out to show how the macroscopic equations resulting from the underlying model can mimic a biologically consistent scenario, where epithelial cells tend to stay aggregated via homotypic adhesion, while mesenchymal cells diffuse through the sample.

The following notations hold:

- Independent variables $t \in \mathbb{R}^+$, $\mathbf{x} \in \mathbb{R}^2$ and $\mathbf{v} \in V \subset \mathbb{R}^2$ denote, respectively, time, position and velocity. The space domain is identified with the whole set $\mathbb{R}^2$, since we normalize $\mathbf{x}$ with respect to the average cellular size, which is much smaller than the size of the whole area where cells can move. The set V of all admissible velocities is defined as a compact and spherically symmetric set of measure $|V|$.

- The phase space densities $f_1(t, \mathbf{x}, \mathbf{v}) \geq 0$ and $f_2(t, \mathbf{x}, \mathbf{v}) \geq 0$ refer, respectively, to epithelial and mesenchymal cells in motion, function $n_3(t, \mathbf{x}) \geq 0$ stands for the density of epithelial cells at rest due to homotypic adhesion and function $n_4(t, \mathbf{x}) \geq 0$ models the density of cytokines that influence cell motion.

- The local densities related to $f_1(t, \mathbf{x}, \mathbf{v})$ and $f_2(t, \mathbf{x}, \mathbf{v})$ and their summation with $n_3(t, \mathbf{x})$ are denoted, respectively, as follows:

$$\varrho_i(t, \mathbf{x}) = \int_V f_i(t, \mathbf{x}, \mathbf{v}) d\mathbf{v}, \quad i = 1, 2, \qquad \varrho(t, \mathbf{x}) = \sum_{i=1}^{3} n_i(t, \mathbf{x}). \tag{9.1}$$

- Cells proliferate at rate $\kappa \in \mathbb{R}^+$ and die through competition for space and resources at rate $\mu \in \mathbb{R}^+$. On the other hand, cytokines regulating cell motion are produced by the cells themselves at a unitary rate, diffuse with a unitary diffusion constant and decay over time at rate $\lambda \in \mathbb{R}^+$.

Our attention is focused on the Cauchy Problem derived by endowing the following set of differential equations

$$\begin{cases} \varepsilon^2 \partial_t f_{1\varepsilon}(t, \mathbf{x}, \mathbf{v}) + \varepsilon \mathbf{v} \cdot \nabla_{\mathbf{x}} f_{1\varepsilon}(t, \mathbf{x}, \mathbf{v}) = \mathcal{F}_{1\varepsilon}[f_{2\varepsilon}, n_{3\varepsilon}, n_{4\varepsilon}](f_{1\varepsilon}) \\ \varepsilon^2 \partial_t f_{2\varepsilon}(t, \mathbf{x}, \mathbf{v}) + \varepsilon \mathbf{v} \cdot \nabla_{\mathbf{x}} f_{2\varepsilon}(t, \mathbf{x}, \mathbf{v}) = \mathcal{F}_{2\varepsilon}[f_{1\varepsilon}, n_{3\varepsilon}, n_{4\varepsilon}](f_{2\varepsilon}) \\ \varepsilon^2 \partial_t n_{3\varepsilon}(t, \mathbf{x}) = \mathcal{N}_{3\varepsilon}[f_{1\varepsilon}](n_{3\varepsilon}) \\ \partial_t n_{4\varepsilon}(t, \mathbf{x}) = \mathcal{N}_{4\varepsilon}[f_{1\varepsilon}, f_{2\varepsilon}](n_{4\varepsilon}) \end{cases} \tag{9.2}$$

to the following initial conditions

$$f_i(0, \mathbf{x}, \mathbf{v}) \geq 0 \text{ on } \mathbb{R}^2 \times V, \quad f_i(0, \mathbf{x}, \mathbf{v}), \nabla_{\mathbf{x}} f_i(0, \mathbf{x}, \mathbf{v}) \in L^1 \cap L^\infty(\mathbb{R}^2 \times V), \tag{9.3}$$

for $i = 1, 2$,

$$n_3(0, \mathbf{x}) \geq 0, \ \forall x \in \mathbb{R}^2, \quad n_3(0, \mathbf{x}), \nabla_{\mathbf{x}} n_3(0, \mathbf{x}) \in L^1 \cap L^\infty(\mathbb{R}^2), \tag{9.4}$$

$$\|\varrho(0, \cdot)\|_{L^1(\mathbb{R}^2)} < \frac{\kappa}{\mu}, \qquad n_4(0, \mathbf{x}) = 0, \ \forall \mathbf{x} \in \mathbb{R}^2, \tag{9.5}$$

as well as to the definitions given hereafter:

$$\mathcal{F}_{1\varepsilon}[f_{2\varepsilon}, n_{3\varepsilon}, n_{4\varepsilon}](f_{1\varepsilon}) = \overbrace{\left(\kappa - \mu \int_X \varrho_\varepsilon(t,\mathbf{x})d\mathbf{x}\right) f_{1\varepsilon}(t,\mathbf{x},\mathbf{v})}^{\text{proliferation and competition}}$$

$$+ \overbrace{\left(\frac{1}{|V|} + \varepsilon\mathbf{v}\cdot\nabla_{\mathbf{x}} n_{4\varepsilon}(t,\mathbf{x})\right)\varrho_{1\varepsilon}(t,\mathbf{x}) - f_{1\varepsilon}(t,\mathbf{x},\mathbf{v})}^{\text{random motion and velocity modification due the cytokines' gradient}}$$

$$+ \overbrace{\varepsilon\frac{(1-\varepsilon)}{|V|}\varrho_{1\varepsilon}(t,\mathbf{x})\varrho_{1\varepsilon}(t,\mathbf{x}) + \varepsilon\frac{(1-\varepsilon)}{|V|}\varrho_{1\varepsilon}(t,\mathbf{x})n_{3\varepsilon}(t,\mathbf{x})}^{\text{velocity modifications due to cell-cell interactions/homotypic adhesion}}$$

$$+ \overbrace{\frac{\varepsilon}{|V|}\varrho_{1\varepsilon}(t,\mathbf{x})\varrho_{2\varepsilon}(t,\mathbf{x}) - \varepsilon\varrho_\varepsilon(t,\mathbf{x})f_{1\varepsilon}(t,\mathbf{x},\mathbf{v})}^{\text{velocity modifications due to cell-cell interactions/homotypic adhesion}} \quad ,$$

$$\mathcal{F}_{2\varepsilon}[f_{1\varepsilon}, n_{3\varepsilon}, n_{4\varepsilon}](f_{2\varepsilon}) = \overbrace{\left(\kappa - \mu \int_X \varrho_\varepsilon(t,\mathbf{x})d\mathbf{x}\right)\varrho_{2\varepsilon}(t,\mathbf{x},\mathbf{v})}^{\text{proliferation and competition}}$$

$$+ \overbrace{\left(\frac{1}{|V|} + \varepsilon\mathbf{v}\cdot\nabla_{\mathbf{x}} n_{4\varepsilon}(t,\mathbf{x})\right)\varrho_{2\varepsilon}(t,\mathbf{x}) - f_{2\varepsilon}(t,\mathbf{x},\mathbf{v})}^{\text{random motion and velocity modification due the cytokines' gradient}}$$

$$+ \overbrace{\frac{\varepsilon}{|V|}\varrho_\varepsilon(t,\mathbf{x})\varrho_{2\varepsilon}(t,\mathbf{x}) - \varepsilon\varrho_\varepsilon(t,\mathbf{x})f_{2\varepsilon}(t,\mathbf{x},\mathbf{v})}^{\text{velocity modifications due to cell-cell interactions}} \quad ,$$

$$\mathcal{N}_{3\varepsilon}[f_{1\varepsilon}](n_{3\varepsilon}) = \overbrace{\left(\kappa - \mu \int_X \varrho_\varepsilon(t,\mathbf{x})d\mathbf{x}\right) n_{3\varepsilon}(t,\mathbf{x})}^{\text{proliferation and competition}} + \overbrace{\varepsilon^2(\varrho_{1\varepsilon}(t,\mathbf{x}) + n_{3\varepsilon}(t,\mathbf{x}))\varrho_{1\varepsilon}(t,\mathbf{x})}^{\text{homotypic adhesion}},$$

$$\mathcal{N}_{4\varepsilon}[f_{1\varepsilon}, f_{2\varepsilon}](n_{4\varepsilon}) = \overbrace{\varrho_\varepsilon(t,\mathbf{x}) + \Delta_{\mathbf{x}} n_{4\varepsilon}(t,\mathbf{x})}^{\text{secretion and diffusion}} - \overbrace{\lambda n_{4\varepsilon}(t,\mathbf{x})}^{\text{decay}}.$$

In particular, following closely the calculations developed in [18], we carry out formally the limit $\varepsilon \to 0$ in the set of equations (9.2), with the aim of deriving the equations for the leading order terms provided by the asymptotic expansions given hereafter:

$$f_{i\varepsilon}(t,\mathbf{x},\mathbf{v}) = f_i^0(t,\mathbf{x},\mathbf{v}) + \varepsilon f_i^1(t,\mathbf{x},\mathbf{v}) + \mathcal{O}(\varepsilon^2), \qquad i = 1,2, \tag{9.6}$$

$$n_{i\varepsilon}(t,\mathbf{x}) = n_i^0(t,x) + \varepsilon n_i^1(t,\mathbf{x}) + \mathcal{O}(\varepsilon^2), \qquad i = 3,4, \tag{9.7}$$

with

$$\varrho_i^0(t,\mathbf{x}) = \int_V f_i^0(t,\mathbf{x},\mathbf{v})d\mathbf{v}, \quad i = 1,2.$$

Let us notice that identities (9.6), (9.7) imply

$$\varrho_\varepsilon(t,\mathbf{x}) = \varrho^0(t,\mathbf{x}) + \varepsilon\varrho^1(t,\mathbf{x}) + \mathcal{O}(\varepsilon^2), \tag{9.8}$$

where, since we assume initial conditions (9.3)-(9.5) to hold,

$$\varrho^0(0,\mathbf{x}) = \int_V f_1(0,\mathbf{x},\mathbf{v}) + f_2(0,\mathbf{x},\mathbf{v})d\mathbf{v} + n_3(0,\mathbf{x}).$$

9.2 Main results

The obtained results are summarized by the following

Theorem 9.2.1 *There exists $\tau > 0$ independent from ε such that the formal limits for $\varepsilon \to 0$ of Eqs.* (9.2) *with initial conditions* (9.3)-(9.5) *can be written, for all $t \in (0,\tau]$ apart from an initial layer, as the convection- diffusion equation*

$$\partial_t\varrho_2^0(t,\mathbf{x}) + \nabla_\mathbf{x}\cdot\left(D\nabla_\mathbf{x}\varrho_2^0(t,\mathbf{x}) - \Gamma[n_4^0]\varrho_2^0(t,\mathbf{x})\right) = 0, \tag{9.9}$$

with diffusivity tensor and convection field defined as

$$D := \frac{1}{|V|}\int_V |\mathbf{v}|^2 d\mathbf{v}, \qquad \Gamma[n_4^0] := \int_V \mathbf{v}(\mathbf{v}\cdot\nabla_\mathbf{x} n_4^0(t,\mathbf{x}))d\mathbf{v}, \tag{9.10}$$

coupled to the following identities

$$\varrho_1^0(t,\mathbf{x}) = 0, \quad \int_{\mathbb{R}^2} \varrho_2^0(t,\mathbf{x}) + n_3^0(t,\mathbf{x})d\mathbf{x} = \frac{\kappa}{\mu}, \tag{9.11}$$

$$n_4^0(t,\mathbf{x}) = \int_0^t\int_{\mathbb{R}^2} \frac{1}{4\pi s} e^{-\frac{|\mathbf{x}|^2}{4s}-\lambda s}\left[\varrho_2^0(t-s,\mathbf{x}-\mathbf{y}) + n_3^0(t-s,\mathbf{x}-\mathbf{y})\right]d\mathbf{y}ds \tag{9.12}$$

and to the additional conditions

$$\varrho_i^0(0,\mathbf{x}) \geq 0 \text{ on } \mathbb{R}^2, \quad \varrho_i^0(0,\mathbf{x}), \nabla_\mathbf{x}\varrho_i^0(0,\mathbf{x}) \in L^1\cap L^\infty(\mathbb{R}^2), \quad i = 1,2,$$

$$n_3^0(0,\mathbf{x}) \geq 0 \text{ on } \mathbb{R}^2, \quad n_3^0(0,\mathbf{x}), \nabla_\mathbf{x} n_3^0(0,\mathbf{x}) \in L^1\cap L^\infty(\mathbb{R}^2),$$

$$\|\varrho^0(0,\cdot)\|_{L^1(\mathbb{R}^2)} < \frac{\kappa}{\mu}, \quad n_4^0(0,\mathbf{x}) = 0, \ \forall\mathbf{x}\in\mathbb{R}^2.$$

Macroscopic equations (9.9),(9.11) and (9.12) established by Theorem 9.2.1 can be interpreted more directly than the underlying system of equations (9.2) and support the idea that the latter can effectively reproduce a biological consistent scenario where epithelial cells adhere to one another via homotypic adhesion, i.e. $n_{10}(t,\mathbf{x}) = 0$ for $t \in (0,\tau]$, while mesenchymal cells tend to diffuse through the sample, i.e. $n_{20}(t,x)$ evolves according to Eq.(9.9) for $t \in (0,\tau]$.

Chapter 10

Recognition and learning in a mathematical model for immune response against cancer [A3]

10.1 Motivations and model

Cancer cells are native to the host body and substantially indistinguishable from normal cells. However, evidence is rapidly accumulating that T-cells contribute to the body multi-layered defenses against tumors. In more detail, T-cells are lymphocytes that carry receptor molecules on their surface, which can recognize the antigens expressed by foreign agents, such as tumor cells, that are presented to them by specialized cells of the immune system, the Antigen Presenting Cells (APCs).

The recognition process involving antigen presenting cells is not strictly selective, i.e. APCs are able to recognize cancer cells expressing several different antigens; however, each APC can present only a finite set of antigens at a time. On the other, the recognition process involving T-cells is very selective and each T-cell is mainly able to recognize only a specific antigen, i.e. its cognate antigen. When an APC detects a cancer cell, the related antigen is presented to naïve T-cells. Thus, those naïve T-cells that recognize this antigen as their cognate one became active. Activated T-cells start to proliferate (i.e. a clonal expansion of activated T-cells occurs) and, through a complex process chain, they become able to selectively recognize and attack cancer cells that express the cognate antigen. Here we consider the effects of *in situ* clonal expansion only. Due to clonal expansion, the number of T-cells being able to destroy the detected cancer cell is greatly increased, and a certain number of them survive even after the eventual defeat of cancerous cells, thus allowing a quicker response in case

of the formation of new cancer cells. As a result, T-cells retain memories of their past experiences and are able to learn from their encounters with foreign agents, in general, and with cancer cells, in particular.

This paper presents a mathematical model for immune response against cancer aimed at reproducing some phenomena emerging from the interactions between tumor and immune cells. In particular, the focus is on evolutionary aspects related to the iterative selection exerted by the immune system over cancer cells, which include recognition, learning and memory aspects of immune response.

The reference system is defined by a sample composed of cancer cells, T-Cells and APCs. The phenomena under consideration include genetic mutations that drive cancer cells to modify their antigenic expressions, proliferation of cancer cells and competition for resources, recognition of cancer cells and antigen-presentation by APCs, activation of naïve T-Cells, clonal expansion of activated TCs and destruction of cancer cells.

We assume such system to be divided into five subpopulations labeled by index $i = 1, ..., 5$: cancer cells ($i = 1$), APCs that are not exposing any antigen on their surface ($i = 2$), APCs that are exposing a certain antigen ($i = 3$), naïve TCs ($i = 4$), and activated TCs ($i = 5$). Apart from subpopulation $i = 2$, which is an unstructured one, the other subpopulations are assumed to be structured by a real continuous variable $s \in S := [0, 1]$, whose biological meaning varies from one subpopulation to another:

- subpopulation $i = 1$: s models the antigenic expression of cancer cells;
- subpopulation $i = 3$: s identifies the antigen exposed by APCs;
- subpopulation $i = 4$: s stands for the cognate antigen of naïve TCs;
- subpopulation $i = 5$: s represents the antigen that an activated TC can effectively attack.

The state of subpopulation $i = 2$ is modeled, at time t, by function

$$n_2 : \mathbb{R}^+ \to \mathbb{R}^+,$$

while the states of subpopulations $i \neq 2$ are characterized, at time t, by functions

$$f_i : \mathbb{R}^+ \times S \to \mathbb{R}^+, \quad i \neq 2,$$

so that the number density of subpopulation $i \neq 2$ at time t can be computed as:

$$\varrho_i(t) = \int_S f_i(t, s)ds. \tag{10.1}$$

The time variable t is assumed to be normalized with respect to the average life-cycle of cancer cells.

The dynamics of the system is described through the following Cauchy Problem

$$\begin{cases} \partial_t \mathbf{h}(t,s) = \mathcal{H}[\mathbf{h}](t,s), \quad (t,s) \in (0,T] \times S \\ \\ \mathbf{h}(0,s) = \mathbf{h}^0(s), \end{cases} \tag{10.2}$$

where

$$\mathbf{h}(t,s) = (f_1(t,s), n_2(t), f_3(t,s), f_4(t,s), f_5(t,s))$$

and

$$\mathbf{h}^0(s) = (f_1^0(s), n_2^0, f_3^0(s), f_4^0(s), f_5^0(s)),$$

with

$$f_i^0(s) \in L^1(S), \quad f_i^0(s) \geq 0 \text{ a.e. on } S, \quad \text{for } i \neq 2, \quad n_2^0 \in \mathbb{R}^+,$$

while $\mathcal{H}$ is componentwise defined by the set of integro-differential equations given hereafter:

$$\begin{aligned}
\partial_t f_1(t,s) &= \underbrace{\int_S M(s-s_*;\varepsilon) f_1(t,s_*) ds_* - f_1(t,s)}_{\text{renewal and mutations}} + \underbrace{\kappa_1(s) f_1(t,s)}_{\text{proliferation}} \\
&- \underbrace{\mu_1(s) f_1(t,s) \varrho_1(t)}_{\text{cell-cell competition}} \underbrace{- \mu^I f_1(t,s) \int_S e^{-\theta^I (s-s^*)^2} f_5(t,s^*) ds^*}_{\text{cancer-immune competition}} \\
d_t n_2(t) &= \underbrace{-\gamma_2 n_2(t) \varrho_1(t) + \mu_3 \varrho_3^2(t)}_{\text{recognition, presentation and homeostatic regulation}} \\
\partial_t f_3(t,s) &= \underbrace{\gamma_2 n_2(t) f_1(t,s) - \mu_3 f_3(t,s) \varrho_3(t)}_{\text{recognition, presentation and homeostatic regulation}} \\
\partial_t f_4(t,s) &= \underbrace{\kappa_4 f_4(t,s) - \mu_4 f_4(t,s) \varrho_4(t)}_{\text{homeostatic regulation}} \underbrace{- \gamma_4 f_4(t,s) \int_S e^{-\theta^I (s-s^*)^2} f_3(t,s^*) ds^*}_{\text{T-cell activation}} \\
\partial_t f_5(t,s) &= \underbrace{\gamma_4 \int_S e^{-\theta^I (s_*-s)^2} f_3(t,s) f_4(t,s_*) ds_*}_{\text{T-cell activation}} + \underbrace{\kappa_5 f_5(t,s) - \mu_5 f_5(t,s) \varrho_5(t)}_{\text{clonal expansion}}.
\end{aligned} \tag{10.3}$$

With reference to Eqs.(10.3), the following definitions and assumptions hold true:

$$M(s-s_*;\varepsilon) := \begin{cases} \gamma_1 \delta(s-(s_* \pm \varepsilon)) + (1-2\gamma_1)\delta(s-s_*), & \text{if } \varepsilon < s < 1-\varepsilon \\ \gamma_1 \delta(s-(s_*-\varepsilon)) + (1-\gamma_1)\delta(s-s_*), & \text{if } 0 \leq s \leq \varepsilon \\ \gamma_1 \delta(s-(s_*+\varepsilon)) + (1-\gamma_1)\delta(s-s_*), & \text{if } 1-\varepsilon \leq s \leq 1, \end{cases}$$

where $\gamma_1 \in \mathbb{R}^+$, δ is the Dirac's delta distribution,

$$\kappa_1 : S \to \mathbb{R}^+, \quad \kappa_1 \in W^{2,\infty}(S), \quad \inf_s \kappa_1(s) > 0 \quad \|\kappa_1(\cdot)\|_{L^\infty(S)} = \kappa^C, \tag{10.4}$$

$$\mu_1 : S \to \mathbb{R}^+, \quad \mu \in W^{2,\infty}(S), \quad \inf_s \mu_1(s) = \mu^C \tag{10.5}$$

and

$$\gamma_2, \gamma_4, \kappa^C, \kappa_4, \kappa_5, \mu_2, \mu_3, \mu_4, \mu_5, \mu^C, \mu^I, \theta^I \in \mathbb{R}^+. \tag{10.6}$$

Since ε is a small real parameter, the above definition for $M(s - s_*; \varepsilon)$ translates into mathematical terms the idea that mutations are small, i.e. only small variations in the antigenic expression can occur from parent to offspring.

10.2 Main results

Standard fixed point arguments can be used to show that Problem (10.2) is well-posed, in the sense of Hadamard, and admits a unique global in time solution.

The asymptotic behavior in time of $\mathbf{h}$ for $\varepsilon \to 0$, i.e. in the limit of small mutations, is characterized by the following theorem, which can be proved by means of standard methods of functional analysis together with some direct computations involving the time derivative of $\mathbf{h}$:

Theorem 10.2.1 *There exists a subsequence of f_i, denoted again as f_i, such that*

$$f_i(t,s) \rightharpoonup f_i^\infty(s) \text{ on } \ w^* - L^\infty((0,T), M^1(S)), \quad \text{as } t \to \infty, \quad \forall i \neq 2.$$

Furthermore, let $\varepsilon \to 0$ and consider functions $\kappa_1(\cdot)$ and $\mu_1(\cdot)$ such that

$$\mathcal{S} = \left\{ s_j \in (\varepsilon, 1-\varepsilon),\ j = 1, ..., J \in \mathbb{N} : \ \frac{\kappa(s_j)}{\mu(s_j)} = \max_s \frac{\kappa_1(s)}{\mu_1(s)} = \frac{\kappa^C}{\mu^C} \right\}, \tag{10.7}$$

assume that function $f_1^0(\cdot)$ satisfies the following conditions

$$\mathcal{S} \subseteq supp(f_1^0(\cdot)), \quad \mathrm{n}_1(0) \leq \frac{\int_S \kappa_1(s) f_1^0(s) ds}{\int_S \mu_1(s) f_1^0(s) ds} \tag{10.8}$$

and make the additional hypothesis given hereafter

$$\mathrm{n}_3(0) = 0, \quad \mu^I = 0, \quad \mathrm{n}_5(0) = 0. \tag{10.9}$$

Then, the following identities hold:

$$f_1^\infty(s) = \sum_{j=1}^J \varrho_{j1} \delta(s - s_j), \quad \sum_{j=1}^J \varrho_{j1} = \frac{\kappa^C}{\mu^C}, \tag{10.10}$$

$$f_3^\infty(u) = \sum_{j=1}^J \varrho_{j3} \delta(s - s_j), \quad \sum_{j=1}^J \varrho_{j3} = \sqrt{\frac{\gamma_2}{\mu_3} \frac{\kappa^C}{\mu^C} n_2^\infty}, \tag{10.11}$$

where $n_2^\infty > 0$ is the asymptotic limit of $n_2(t)$ for $t \to \infty$,

$$supp(f_5^\infty(\cdot)) = \bigcup_{t \in \mathbb{R}^+} supp(f_3(t,\cdot)) \cap supp(f_4(t,\cdot)). \tag{10.12}$$

In order to illustrate and extend analytical results, we numerically solve, under different parameter settings, the Cauchy Problem (10.2). Numerical simulations are performed in MATLAB by means of a collocation method with 200 points on $[0, 1]$. Interval $[0, T]$ is selected as time domain, where T is an integer multiple of the unit time $dt = 0.005$. In particular, we set $\varepsilon = 0.003$ (i.e. $\varepsilon \to 0$), we assume function μ to be identically equal to a constant value and

$$\kappa_1(s) := \kappa^C e^{-\frac{[(s-0.35)^2+(s-0.65)^2]}{0.001}}, \tag{10.13}$$

i.e. those cells that express the antigens corresponding to $s = 0.35$ and $s = 0.65$ can proliferate with the highest rate, or

$$\kappa_1(s) := \kappa^C, \quad \forall s \in S, \tag{10.14}$$

i.e. all cancer cells proliferate with the same rate independently from their antigenic expression.

Numerical simulations are meant to:

- test the capability of the model to reproduce and justify emerging behaviors depicted by laboratory experiments;
- verify the ability of the model to reproduce immune recognition and learning processes;
- analyze the effects of intra-tumor heterogeneity on immune response against cancer.

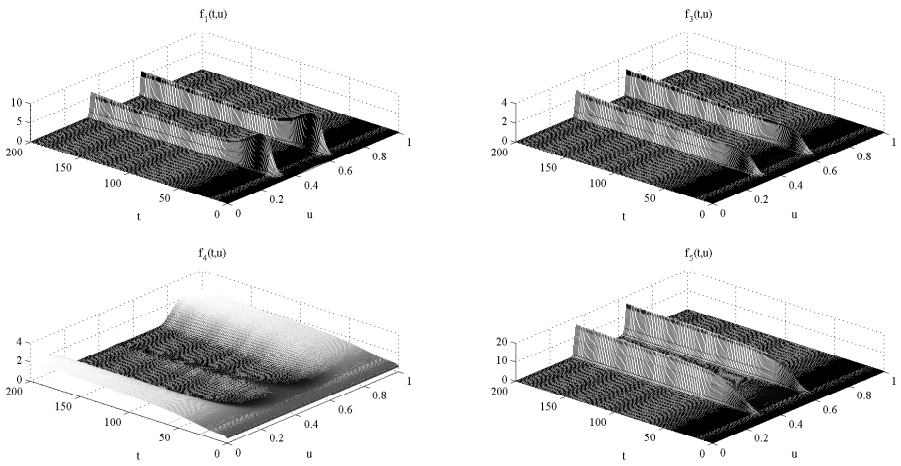

Figure 10.1: Dynamics of $f_1(t,s)$, $f_3(t,s)$, $f_4(t,s)$ and $f_5(t,s)$ in the limit $\varepsilon \to 0$. Function $f_1(t,s)$ concentrates, across time, around the points where $\kappa_1(s)$ (i.e. the probability for cell proliferation) attains its maximum. After an initial transient, $f_3(t,s)$ replicates the distribution of $f_1(t,s)$ over S, while $f_5(t,s)$ replicates the instantaneous distribution of $f_3(t,s)$ keeping memory of the past configurations. These results support the idea that the present model is able to mimic both the action of immune cells against cancer cells, in general, and the recognition, learning and memory aspects related to immune response, in particular.

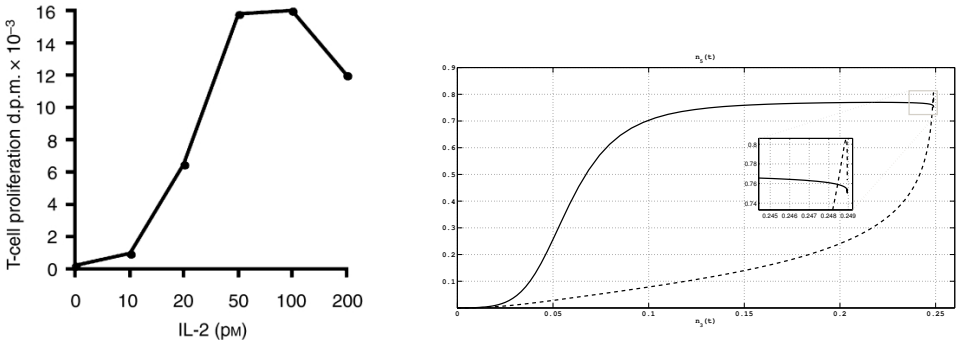

Figure 10.2: **Left panel.** Experimental trends of the response of T-cells to activation stimuli (figure reproduced from [15]). **Right panel.** Dynamics of $\varrho_5(t)$ vs $\varrho_3(t)$ for $\kappa_5 > \kappa_4$ and $\mu_5 > \mu_4$ (solid line), i.e. the dynamics of the activated TCs is assumed to be faster than the one of naïve TCs, or $\kappa_4 > \kappa_5$ and $\mu_4 > \mu_5$ (dashed line), i.e. the dynamics of activated TCs is assumed to be slower than the one of naïve TCs, with γ_4 fixed and $\varepsilon \to 0$. As long as $\varrho_3(t)$ does not overcome a certain threshold value, the growth of $\varrho_5(t)$ is slow. On the other hand, when $\varrho_3(t)$ crosses the threshold, $\varrho_5(t)$ increases in a faster way.

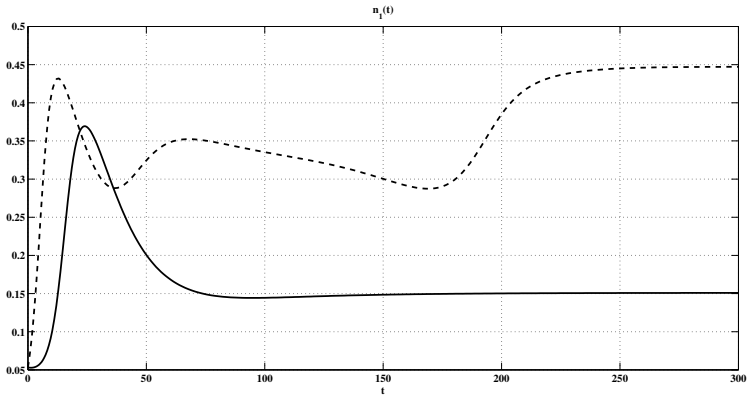

Figure 10.3: Dynamics of $\varrho_1(t)$ under definition (10.13) (solid line) and definition (10.14) (dashed line) in the limit $\varepsilon \to 0$. The saturation value of $\varrho_1(t)$ is higher under (10.14) rather than under (10.13). Since (10.14) refers to the situation where all the cells are characterized by the same probability for proliferating, and thus surviving, independently from their antigenic expressions (i.e. intra-tumor heterogeneity is potentially higher), this result suggests that immune response becomes less effective as long as the set of antigens expressed by cancer cells gets wider.

Chapter 11

A mathematical model for immune and autoimmune response mediated by T-cells [A12]

11.1 Motivations and model

Human body is protected against infectious agents by the immune system, which is composed of different cells and several molecules providing a strong defense against pathogens. Among immune cells, T-cells carry receptor molecules on their surface, which can recognize non-self antigens that are presented to them by specialized cells of the immune system, the Antigen Presenting Cells (APCs). The recognition process involving antigen presenting cells is not strictly selective, i.e. APCs are able to recognize several different antigens; however, each APC can present only a finite set of antigens at a time. On the other hand, the recognition process involving T-cells is very selective and each T-cell is mainly able to recognize a specific antigen, i.e. its cognate antigen.

When an APC detects a foreign antigen, this is presented to naïve T-cells. Thus, those naïve T-cells that recognize this antigen as their cognate one become active. Activated T-cells start to proliferate (i.e. they undergo clonal expansion) and differentiate into effector T-cells. Effector T-cells act by eliminating the target antigen and are led to apoptosis by specific molecules, whose production is stimulated along with T-cells activation. In this way, after the elimination of non-self pathogens, the number of effector T-cells is highly reduced through cell death, i.e. immune response is switched-off [14]. However, some T-cells survive from this switching-off and become memory T-cells remaining within the peripheral tissues and circulation for an extended time after the elimination of infectious agents, ready to respond to the same antigen upon future exposures

and making immune response to this antigen faster and more efficient. As a result, the immune system learns from its past experiences and immunological memory is developed, which allows a quick response to a subsequent encounter with the same pathogen. Such a process is called immunization.

The inability of the immune system to distinguish between host and foreign/infected entities (i.e. self and non-self agents [43]) leads to the elicitation of immune cells (i.e. leukocytes or white blood cells) toward host components. Such a process is called autoreactivity and causes the development of the so-called autoimmunity.

The etiology of autoimmunity is multifactorial. Among others genetic susceptibility, molecular mimicry and somatic genetic mutations are all considered important in its development. In particular, an individual can be born with a genetic makeup that makes her/him more prone to develop autoimmunity and some genes confer a level of risk much higher than others; molecular mimicry occurs when T-cells react against self antigens having a sequence similarity with a non-self antigen, so that cross-reactivity can take place; genetic factors can be crucial determinant of autoimmunity as testified, for instance, by Autoimmune LymphoProliferative Syndrome (ALPS), which is caused by genetic defects leading to autoreactivity by causing inability to trigger apoptosis of activated T-cells [43].

The main goal of this paper consists in defining a mathematical model able to mimic the action of the immune system against both self and non-self agents and the initiation of auto-reactivity, with particular reference to the roles played by T-cells. The reference system is defined by a sample composed of self cells, non-self cells and immune cells. With the aim of modeling the action of the immune system against self and non-self antigens as well as the initiation of auto-reactivity, we include in the model homeostatic proliferation and death of self and non-self cells, antigen-presentation by APCs, recognition and activation processes involving naïve T-Cells (TCs), clonal expansion of activated TCs, immune action against foreign cells, autoimmune action of activated TCs over host cells, immunization and autoimmunization.

The multicellular system under consideration is assumed to be divided into six subpopulations labeled by index i: host cells ($i = 1$), i.e. cells that express self antigens only, foreign cells ($i = 2$), i.e. cells that express non-self antigens, APCs that are not exposing any antigen on their surface ($i = 3$), APCs that are exposing a certain antigen ($i = 4$), naïve TCs ($i = 5$), activated TCs ($i = 6$). Apart from subpopulation $i = 3$, which is an unstructured one, subpopulations $i = 1, 2, 4, 5, 6$ are assumed to be structured by a real continuous variable $s \in S := [0, 1]$, whose biological meaning varies from one subpopulation to another:

- subpopulation $i = 1$: s models the antigenic expression of host cells;

- subpopulation $i = 2$: s is the antigenic expression of foreign cells;

- subpopulation $i = 4$: s identifies the antigen exposed by APCs;

- subpopulation $i = 5$: s stands for the cognate antigen of naïve TCs;

- subpopulation $i = 6$: s represents the target antigen of each activated TC.

The state of subpopulation $i = 3$ is modeled, at time t, by function

$$n_3 = n_3(t),$$

while the states of subpopulations $i \neq 3$ are characterized, at time t, by functions

$$f_i = f_i(t, s), \quad i \neq 3,$$

so that the number densities of subpopulations $i \neq 3$ at time t can be computed as:

$$\varrho_i(t) = \int_S f_i(t, s) ds. \tag{11.1}$$

The time variable t is assumed to be normalized with respect to the average life-cycle of host and foreign cells.

The dynamics of the system is described through the Cauchy Problem defined by endowing the following set of integro-differential equations with proper initial conditions:

$$\begin{aligned}
\partial_t f_1(t,s) &= \underbrace{\kappa^C f_1(t,s) - \mu^C f_1(t,s)(\varrho_1(t) + \varrho_2(t))}_{\text{homeostatic proliferation and death}} - \underbrace{\xi_1 f_1(t,s) \int_S e^{-\theta^C (s-s^*)^2} f_6(t,s^*) ds^*}_{\text{autoimmune action}} \\
\partial_t f_2(t,s) &= \underbrace{\kappa^C f_2(t,s) - \mu^C f_2(t,s)(\varrho_1(t) + \varrho_2(t))}_{\text{homeostatic proliferation and death}} - \underbrace{\xi_2 f_2(t,s) \int_S e^{-\theta^C (s-s^*)^2} f_6(t,s^*) ds^*}_{\text{immune action}} \\
d_t n_3(t) &= \underbrace{-n_3(t) \sum_{k=1}^{2} \int_U \gamma_k(s^*) f_k(t,s^*) ds^* + \mu_4 \varrho_4^2(t)}_{\text{recognition, presentation and regulation}} \\
\partial_t f_4(t,s) &= \underbrace{n_3(t) \sum_{k=1}^{2} \gamma_k(s) f_k(t,s) - \mu_4 f_4(t,s) \varrho_4(t)}_{\text{recognition, presentation and regulation}} \\
\partial_t f_5(t,s) &= \underbrace{\kappa_5 f_5(t,s) - \mu_5 f_5(t,s) \varrho_5(t)}_{\text{regulation}} - \underbrace{\gamma_5(s) f_5(t,s) \int_S e^{-\theta^C (s-s^*)^2} f_4(t,s^*) ds^*}_{\text{T-cell activation}} \\
\partial_t f_6(t,s) &= \underbrace{f_4(t,s) \int_S e^{-\theta^C (s-s_*)^2} \gamma_5(s_*) f_5(t,s_*) ds_*}_{\text{T-cell activation}} + \underbrace{\kappa_6 f_6(t,s) - \mu_6 f_6(t,s) \varrho_6(t)}_{\text{clonal expansion}} \\
&+ \underbrace{f_6(t,s) \sum_{k=1}^{2} \lambda_k \int_S e^{-\theta^C (s-s^*)^2} f_k(t,s^*) ds^*}_{\text{immunization and autoimmunization}}.
\end{aligned} \tag{11.2}$$

Functions $\gamma_1(s)$, $\gamma_2(s)$ and $\gamma_5(s)$ can be assumed to be real Lipschitz continuous and such that

$$\max_{s\in S}\gamma_1(s)=\gamma_1^C,\quad \max_{s\in S}\gamma_2(s)=\max_{s\in S}\gamma_5(s)=\gamma^C,$$

while all the other parameters of the model are assumed to be non-negative real numbers.

11.2 Main results

As previously noted, molecular mimicry, genetic susceptibility and somatic genetic mutations act, among others, as key players in the development of autoimmune diseases. Therefore, it is worth noting that the above described modeling strategies allow to include these factors in the dynamics of the reference sample. In fact:

- the effects of molecular mimicry can be taken into account by assigning to parameters γ_1^C (i.e. the maximum of the probability for the presentation of self antigens), ξ_1 (i.e. the probability for autoimmune destruction) and λ_1 (i.e. the probability for autoimmunization) some non-zero values;
- the action of genetic susceptibility, which makes the presentation and recognition abilities of APCs and naïve TCs to be mainly focused over certain antigens, can be modeled by defining $\gamma_2(s)$ (i.e. the probability for the presentation of non-self antigens) and $\gamma_5(s)$ (i.e. the probability for recognition and activation phenomena involving naïve T-cells) so that the related maximum value γ^C is attained only on a countable subset of S;
- the effects of those genetic alterations that cause an over-proliferation of T-cells and a reduced cytotoxic activity can be included by reducing the values of parameters μ_6 (i.e. the probability for the programmed death of activated T-cells) and ξ_2 (i.e. the probability for immune destruction).

This is highlighted by the following figures, which summarize the results of numerical simulations performed in MATLAB by means of a collocation method with 200 points on $[0,1]$. Interval $[0,T]$ is selected as time domain, where T is an integer multiple of the unit time $dt=0.005$.

Along all simulations, the expressions of functions $\gamma_1(s)$, $\gamma_2(s)$ and $\gamma_5(s)$ are chosen among the ones given hereafter:

$$\gamma_1(s):=\gamma_1^C e^{-\frac{[(s-0.1)^2+(s-0.9)^2]}{0.01}},\quad \gamma_2(s)=\gamma_5(s):=\gamma^C e^{-\frac{[(s-0.1)^2+(s-0.9)^2]}{0.01}},\ (11.3)$$

i.e. the antigens identified by $u=0.1$ and $u=0.9$ are the ones most presented by APCs and most recognized by naïve TCs,

$$\gamma_1(s):=\gamma_1^C,\quad \gamma_2(s)=\gamma_5(s):=\gamma^C,\qquad (11.4)$$

i.e. all the possible antigens are presented by APCs and recognized by naïve TCs with the same probability.

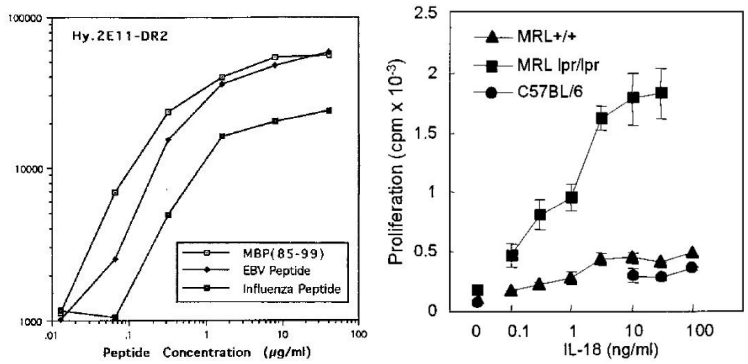

Figure 11.1: **Left panel.** Experimental trends for T-cells activated against certain non-self antigens (•, ■) and T-cells acting over a self antigen similar to the non-self ones (□) in presence of molecular mimicry. The concentrations of T-cells is plotted as a function of antigens concentrations (figure reproduced from [73]). **Right panel.** Comparison between experimental trends of the T-cells response to activation stimuli in absence (•, ▲) and in presence (■) of somatic genetic mutations (figure reproduced from [55]).

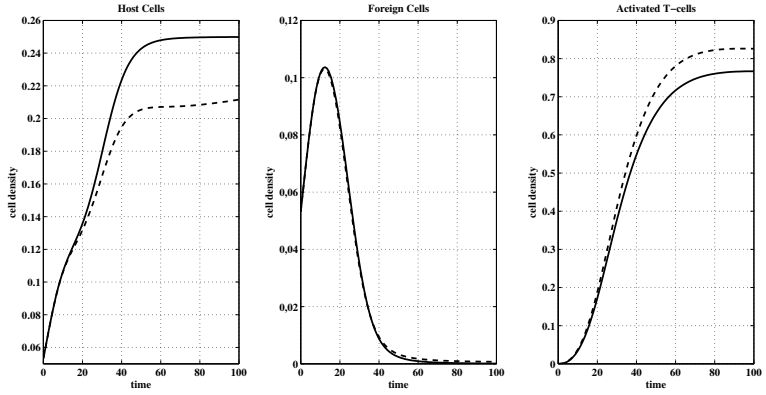

Figure 11.2: Dynamics of $\varrho_1(t)$ (left), $\varrho_2(t)$ (center) and $\varrho_6(t)$ (right) for $\gamma_1^C = \lambda_1 = \xi_1 = 0$ (fixed lines) or $\gamma_1^C \neq 0$, $\lambda_1 \neq 0$ and $\xi_1 \neq 0$ (dashed lines). Fixed lines refer to normal conditions, while dashed lines are obtained in presence of molecular mimicry and highlight over-proliferation of T-cells and over-reactivity against host cells. The trends of $\varrho_1(t)$ are in good qualitative agreement with the experimental ones depicted by Figure 11.1.

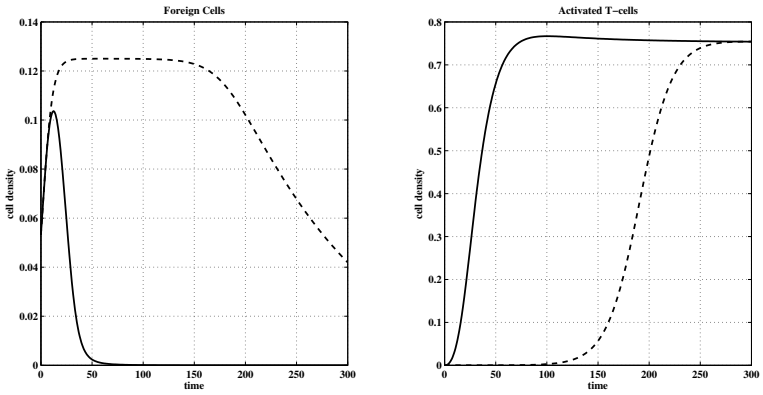

Figure 11.3: Dynamics of $\varrho_2(t)$ (left) and $\varrho_6(t)$ (right) with $\gamma_1(s)$, $\gamma_2(s)$ and $\gamma_5(s)$ defined by (11.3) (fixed lines) or by (11.4) (dashed lines). In both the cases $\gamma_1^C = \lambda_1 = \xi_1 = 0$. Fixed lines refer to normal conditions, while dashed lines are obtained in presence of genetic susceptibility, which makes the presentation and recognition abilities of APCs and naïve TCs to be focused over certain antigens. This figure points out how genetic susceptibility can introduce a delay in the activation of T-cells in those cases where APCs and naïve TCs are mainly able, respectively, to present and recognize certain antigens, which are not the ones most expressed by foreign cells.

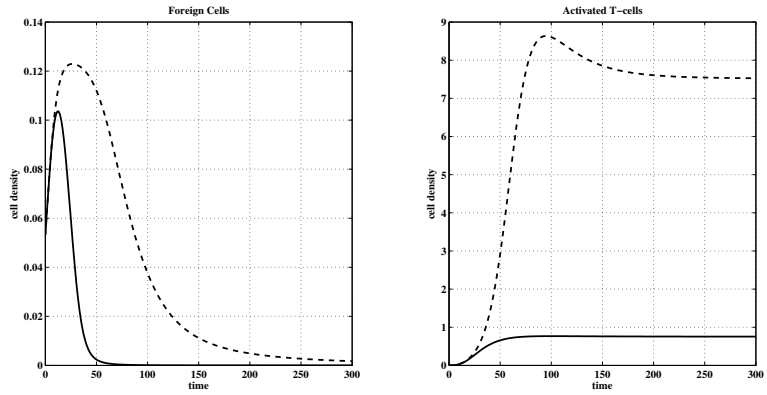

Figure 11.4: Dynamics of $\varrho_2(t)$ (left) and $\varrho_6(t)$ (right). Fixed lines refer to some values of ξ_2 and μ_6 that are higher than the ones related to dashed lines. In both the cases $\gamma_1^C = \lambda_1 = \xi_1 = 0$. Fixed lines are related to normal conditions, while dashed lines are obtained in presence of genetic alterations that cause an over-proliferation of T-cells and a reduced cytotoxic activity. The trends shown by the figure on the right are in good qualitative agreement with the experimental ones depicted by Figure 11.1.

Chapter 12

Populational adaptive evolution, chemotherapeutic resistance and multiple anti-cancer therapies [A4]

12.1 Motivations and model

Depending on the nature of the tumor, different therapies can be used in combination with one other in order to reduce the probability of resistance emergence along with the side-effects on healthy cells [64]. In particular, besides cytotoxic drugs, here we focus on an additional class of therapeutic agents, the so-called cytostatic drugs, which act by slowing down cancer cell proliferation and tumor growth. Cytostatic drugs have lower toxicity for healthy cells and reduce the emergence of resistance, which usually follows from treatments with cytotoxic drugs. In fact, they allow the survival of a small number of chemosensitive cells, which can reduce the growth of resistant clones through competition for space and resources.

Motivated by the theory of mutation-selection in adaptive evolution, we propose a mathematical model describing the selection/mutation dynamics of healthy and tumor cells under the effects of cytotoxic and cytostatic drugs.

The reference system is defined by a well-mixed sample composed of healthy and cancer cells, which are grouped, for modeling purposes, into two subpopulations labeled, respectively, by index $i = 1, 2$. The two subpopulations are structured by a real continuous variable $s \in S := [0, 1]$ standing for the gene resistance expression level. In the sequel we will use the term gene expression

meaning not only expression of one supposed resistance gene, but more generally of several genes yielding together a continuous drug resistance phenotype.

The state of the system at time t is described by functions $f_1(t,s)$ and $f_2(t,s)$, whose evolution is ruled by the Cauchy Problem defined by linking the following differential equations to suitable initial conditions

$$\partial_t f_{1,2}(t,s) = \overbrace{\frac{\theta_{1,2}}{1+\alpha_{1,2}g_1(t)}\left(\int r_{1,2}(s_*)M(s_*,s;\varepsilon)f_{1,2}(t,s_*)ds_* - r_{1,2}(s)f_{1,2}(t,s)\right)}^{\text{mutations and renewal}} + \underbrace{\left(\frac{r_{1,2}(s)}{1+\alpha_{1,2}g_1(t)} - d_{1,2}(s)I_{1,2}(t)\right)f_{1,2}(t,s)}_{\text{growth with cytostatic therapies and death}} - \underbrace{g_1(t)\mu_{1,2}(s)f_{1,2}(t,s)}_{\text{effect of cytotoxic therapies}}, \tag{12.1}$$

where $g_1(t)/g_2(t)$ stand for the concentration of cytotoxic/cytostatic drugs at time t and

$$I_1(t) := a_{11}\rho_1(t) + a_{12}\rho_2(t), \qquad I_2(t) := a_{21}\rho_1(t) + a_{22}\rho_2(t). \tag{12.2}$$

The following considerations and hypothesis are assumed to hold:

$$M(\cdot,\cdot;\varepsilon) \geq 0, \quad \int_S M(\cdot,s;\varepsilon)ds = 1, \quad \int_S sM(\cdot,s;\varepsilon)ds = \varepsilon, \quad \forall \varepsilon > 0, \tag{12.3}$$

$$0 \leq \theta_{1,2} < 1, \qquad \mu_{1,2}(\cdot) > 0, \quad \mu'_{1,2}(\cdot) < 0, \quad \mu_1(\cdot) < \mu_2(\cdot), \tag{12.4}$$

$$a_{12}, a_{21} \geq 0, \qquad a_{11} > a_{12}, \quad a_{22} > a_{21}, \tag{12.5}$$

$$r_{1,2}(\cdot) > 0, \qquad r'_{1,2}(\cdot) < 0, \tag{12.6}$$

$$d_{1,2}(\cdot) > 0, \qquad d'_{1,2}(\cdot) < 0, \tag{12.7}$$

$$\alpha_1 < \alpha_2. \tag{12.8}$$

The last one of assumptions (12.3) implies that ε is the average size of mutations, while assumptions (12.4) on functions $\mu_{1,2}$ embody the fact that cytotoxic agents are more effective against cancer than healthy cells and their efficiency is lower on cells expressing higher resistance levels. Assumptions (12.5) mimic a scenario where intra-population interactions occur at a higher rate than inter-population ones; assumptions (12.6) translate into mathematical terms the idea that producing resistance genes implies resource allocation both for healthy and cancer cells; assumptions (12.7) account for the fact that mutations conferring resistance to therapies may also provide cells with stronger competitive abilities. Finally, assumptions (12.8) rely on the idea that cytostatic agents are designed to be more effective against cancer cells rather against the healthy ones.

12.2 Main results

We analyze the model (12.1) through numerical simulations illustrating how the outputs can be influenced by different concentrations of cytotoxic and cytostatic agents. From a biological perspective, this means to use the present model as an *in silico* laboratory to highlight some mechanisms that may play a key role in the development of cancer resistance to therapies, with the aim of providing support to the design of optimal therapeutic strategies. Numerical simulations are performed in MATLAB using an implicit-explicit finite difference scheme with 2000 points on the interval $[0,1]$. Interval $[0,T]$ with $T = 2000dt$ is selected as time domain, where the unit time dt is chosen equal to 0.1.

We choose the initial conditions

$$f_1(t=0,s) = f_2(t=0,s) := C^0 e^{-\frac{(s-0.5)^2}{\varepsilon}}, \qquad \varepsilon = 0.01, \tag{12.9}$$

where C^0 is a positive real constant such that

$$\varrho_1(t=0) + \varrho_2(t=0) \approx 1.$$

Parameter ε is set equal to 0.01 to mimic a biological scenario where most of the cells are characterized by the resistant gene expression level corresponding to $s = 0.5$ at the beginning of observations.

Assumptions and definitions given hereafter are used along all simulations:

$$M(s_*, s; \varepsilon) := C_M e^{-\frac{(s_*-s)^2}{\varepsilon^2}},$$

$$C_M \int_0^1 e^{-\frac{(s_*-s)^2}{\varepsilon^2}} ds = 1, \quad \forall s_* \in [0,1],$$

$$\theta_1 = \theta_2 := 0.1, \qquad r_1(s) := \frac{1.5}{1+s^2}, \quad r_2(s) := \frac{3}{1+s^2}, \qquad \alpha_1 := 0.01, \quad \alpha_2 := 1,$$

$$a_{11} = a_{22} := 1, \quad a_{12} := 0.07 \quad a_{21} := 0.01,$$

$$d_1(s) := 0.5(1-0.1s), \quad d_2(s) := 0.5(1-0.3s),$$

$$\mu_1(s) := \frac{0.2}{0.49+s^2}, \quad \mu_2(s) := \frac{0.4}{0.49+s^2}.$$

Functions $g_1(t)$ and $g_2(t)$ are assumed to be constant, i.e.

$$g_1(t) := g_1 \in \mathbb{R}^+, \qquad g_2(t) := g_2 \in \mathbb{R}^+,$$

and the values of parameters g_1 and g_2 are chosen case by case according to the aim of the analysis.

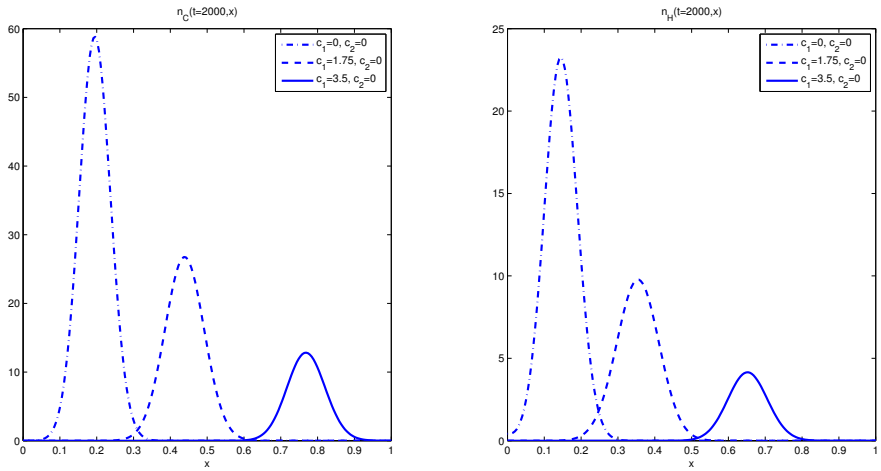

Figure 12.1: Trends of $f_2(t,s)$ (left) and $f_1(t,s)$ (right) at $t = 2000$ for $g_1 = 0$ (dashed-dotted lines), $g_1 = 1.75$ (dashed lines) and $g_1 = 3.5$ (solid lines), in the limit $\varepsilon \to 0$. In all cases, parameter g_2 is set equal to zero. As parameter g_1 increases, functions $f_2(t = 2000, s)$ and $f_1(t = 2000, s)$ tend to be highly concentrated around some increasing values of s and their maximum values become smaller; this indicates higher resistance with higher doses of drug.

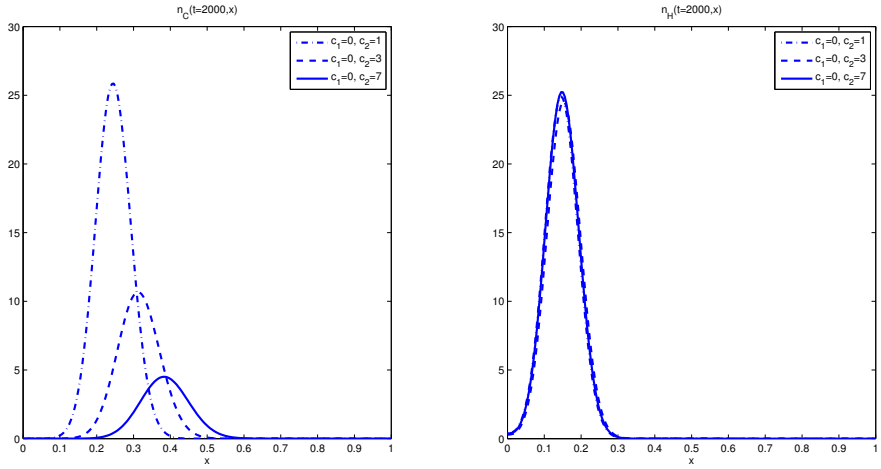

Figure 12.2: Trends of $f_2(t,s)$ (left) and $f_1(t,s)$ (right) at $t = 2000$ for $g_2 = 1$ (dashed-dotted lines), $g_2 = 3$ (dashed lines) and $g_2 = 7$ (solid lines), in the limit $\varepsilon \to 0$. In all cases, parameter g_1 is set equal to zero. Increasing values of parameter g_2 lead the qualitative behavior of function $f_2(t = 2000, s)$ to become closer to the one of $f_2(t = 0, s)$. On the other hand, the trend of function $f_1(t = 2000, s)$ remains basically unaltered.

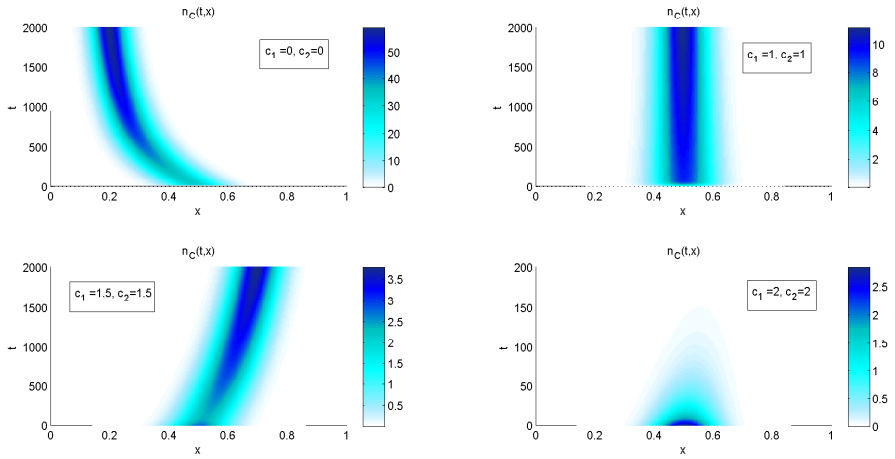

Figure 12.3: Dynamics of $f_2(t,s)$ for $g_1 = g_2 = 0$ (top-left), $g_1 = g_2 = 1$ (top-right), $g_1 = g_2 = 1.5$ (bottom-left) and $g_1 = g_2 = 2$ (bottom-right), in the limit $\varepsilon \to 0$. As long as parameters g_1 and g_2 increase, the maximum value of $f_2(t = 2000, s)$ becomes smaller so that, under the choice $g_1 = g_2 = 2$, function $f_2(t,s)$ tends to zero across time.

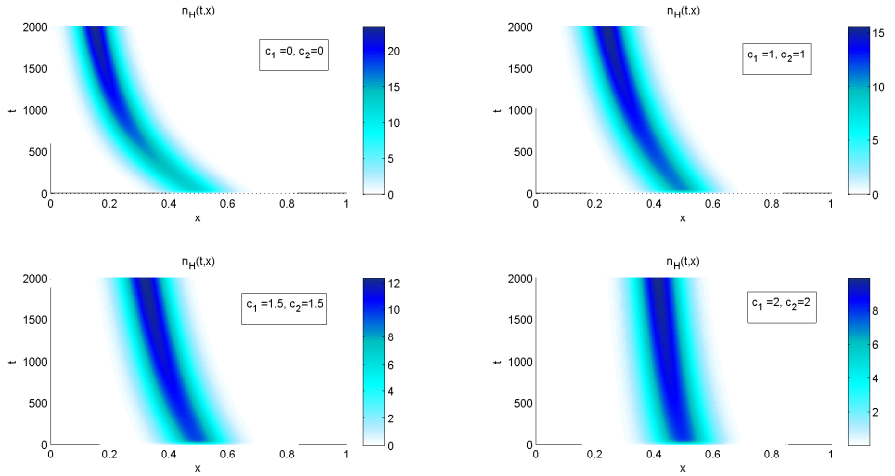

Figure 12.4: Dynamics of $f_1(t,s)$ for $g_1 = g_2 = 0$ (top-left), $g_1 = g_2 = 1$ (top-right), $g_1 = g_2 = 1.5$ (bottom-left) and $g_1 = g_2 = 2$ (bottom-right), in the limit $\varepsilon \to 0$. As long as parameters g_1 and g_2 increase, the maximum value of $f_1(t = 2000, s)$ becomes smaller but about one half of the healthy cells is still alive at the end of computations.

Part V

Models for Socio-Economic Systems

Introduction

"It has been more profitable for us to
bind together in the wrong direction
than to be alone in the right one"
N.N. Taleb, The Black Swan: The Impact of the Highly Improbable

This part focuses on continuous structured population models for opinion formation within socio-economic systems. In more detail,

- Chapter 13 deals with the asymptotic behavior of mathematical models for opinion dynamics under bounded confidence of Deffuant-Weisbuch type. In particular, a theorem establishing the weak convergence of the solution to a sum of Dirac masses and characterizing the concentration points for different values of the model parameters is provided.

- Chapter 14 presents a hybrid model for opinion formation in a large group of agents exposed to the persuasive action of a small number of strong opinion leaders. The model is defined by coupling a finite difference equation for the dynamics of leaders opinion with a continuous integro-differential equation for the dynamics of the others. The asymptotic behavior in time of the related solution is characterized under distinct scenarios, where different emerging behaviors can be observed.

- Chapter 15 introduces a class of integro-differential equations modeling the dynamics of a market where agents are called to estimate the value of a given traded good. Two basic mechanisms are assumed to concur in value estimation: interactions between agents and some sources of public information and herding phenomena. The asymptotic behavior in time of the related solution is characterized for some general parameter settings, which mimic different economic scenarios.

Chapter 13

Asymptotic analysis of continuous opinion dynamics models under bounded confidence [A1]

13.1 Motivations and model

This paper deals with the asymptotic behavior of mathematical models for opinion dynamics under bounded confidence of Deffuant-Weisbuch type, as reviewed in [1, 12, 24, 49, 68] . Such models describe the dynamics of a population structured by a continuous parameter $s \in S \subset \mathbb{R}$ standing for the individuals' opinion with respect to a given statement. The opinion can be contrary ($s < 0$), neutral ($s = 0$) or favorable ($s > 0$) and it evolves through repeated pairwise interactions involving only agents at a distance smaller than a threshold value R, the so-called bound of confidence. In particular, we focus on compromise models (i.e. two interacting agents are supposed to average their current opinions) with homogeneous bound of confidence (i.e. R is assumed to be a real number and not a real function of s), where S is a compact set defined as

$$S := [-n_1 R; n_2 R] \subset \mathbb{R}, \quad \text{with} \;\; R \in \mathbb{R}^+ \quad \text{and} \;\; n_1, n_2 \in \mathbb{R}^+.$$

The density of agents expressing opinion s at time t is modeled by a function $f(t, s)$

$$f : \mathbb{R}^+ \times S \to \mathbb{R}^+,$$

which satisfies the following initial value problem:

$$\begin{cases} \partial_t f(t,s) = \mathcal{Q}[f,f](t,s), \quad s \in S, \quad t > 0 \\ \\ f(0,s) = f^0(s) \in L^1(S), \quad f^0(s) \geq 0 \; a.e. \; on \; S, \quad \int_S f^0(s) ds = 1. \end{cases} \tag{13.1}$$

Functional $\mathcal{Q}[f,f]$ is defined as

$$\begin{aligned}\mathcal{Q}[f,f](t,s) &:= \int_S\int_S \eta(s_*,s^*;R)Q(s|s_*,s^*)f(t,s_*)f(t,s^*)ds_*ds^* \\ &- f(t,s)\int_S \eta(s,s^*;R)f(t,s^*)ds^*, \end{aligned} \tag{13.2}$$

whith:

$$Q(s|s_*,s^*) := \delta\left(s - \frac{s_*+s^*}{2}\right), \qquad \int_S Q(s|s_*,s^*)ds = 1, \tag{13.3}$$

where δ is the Dirac's delta distribution,

$$\eta(s_*,s^*;R) := \mathbf{1}_{\{|s_*-s^*|\le R\}}, \qquad \eta(s_*,s^*;R) = \eta(s^*,s_*;R), \tag{13.4}$$

where $\mathbf{1}$ is the indicator function.

13.2 Main results

At first, we provide a well-posedness and global existence result for the Cauchy Problem (13.1), which can proved, as in the case of kinetic equations for homogeneous granular gases, making use of standard *a priori* estimates and fixed point arguments.

Then, we characterize the qualitative large time behavior of the solution to Problem (13.1). In particular, we prove the convergence of $f(t,s)$ to a non-negative measure in the limit $t \to \infty$ making use of standard techniques of functional analysis. Furthermore, we develop a characterization of such a measure by means of direct computations involving the time derivative of $f(t,s)$ under different choices of S, i.e. for different values of n_1 and n_2 leading to different and not complementary asymptotic scenarios. These results are collected in the following

Theorem 13.2.1 *Let f solve the Cauchy Problem* (13.1)*. Then, there exists a subsequence of f, denoted again as f, such that:*

i) (Establishing convergence)

$$f(t,s) \rightharpoonup f^\infty(s), \quad \text{as } t \to \infty,$$

where f^∞ is a bounded non-negative measure.

ii) (Identifying the limit f^∞)

Case 1 (one single Dirac mass).
If

$$n_1 \le \frac{R-\bar{s}(0)}{R} \quad \text{and} \quad n_2 \le \frac{R+\bar{s}(0)}{R}, \tag{13.5}$$

with

$$\bar{s}(t) = \frac{\int_S s f(t,s) ds}{\varrho(t)},$$

then

$$f^\infty(s) = \delta(s - \bar{s}(0)). \tag{13.6}$$

Case 2 (multiple Dirac masses).
If

$$n_1 = n_2 = n \in \mathbb{N} \quad \textit{and} \quad f^0(s) = \frac{1}{2nR},\ \forall s \in S, \tag{13.7}$$

then

$$f^\infty(s) = \sum_{k=0}^{n-1} \varrho_k \delta(s - \hat{s}_k), \quad \hat{s}_k \in \mathcal{B}(c_k, R/2) \tag{13.8}$$

and

$$\sum_{k=0}^{n-1} \varrho_k = 1, \qquad \sum_{k=0}^{n-1} s_k \varrho_k = 0, \qquad \varrho_a = \varrho_b \quad \textit{if } c_a = -c_b, \tag{13.9}$$

where $k = 0, 1, \ldots, n-1$ *and* $\mathcal{B}(c_k, R/2)$ *denotes the ball of center* $c_k = nR - (2k+1)R$ *and radius* $\dfrac{R}{2}$.

Asymptotic results are illustrated by means of numerical simulations performed in MATLAB making use of a collocation method. With reference to the s variable, a uniform discretization of S consisting of 600 points is selected as computational domain, while the set $[0, T]$ is the reference time domain, where T varies case by case and it is defined as an integer multiple of the time unit $dt = 0.05$.

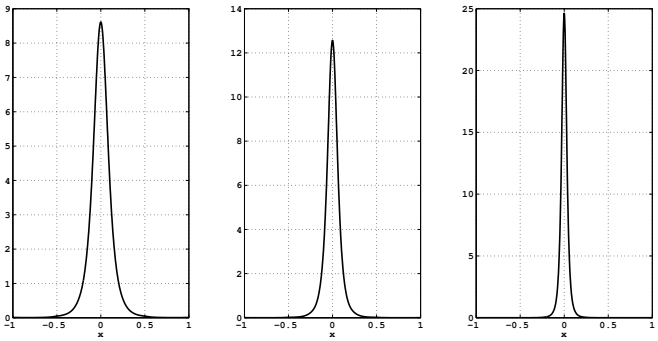

Figure 13.1: Large time behavior of $f(t,s)$ under assumptions (13.5). Simulations are performed with $R = 1$, $n_1 = n_2 = 1$ and for different initial conditions, i.e. $f^0(s) = \frac{1+s^2}{4}$ (left), $f^0(s) = \frac{1}{2}$ (center) and $f^0(s) = \frac{3(1-s^2)}{4}$ (right).

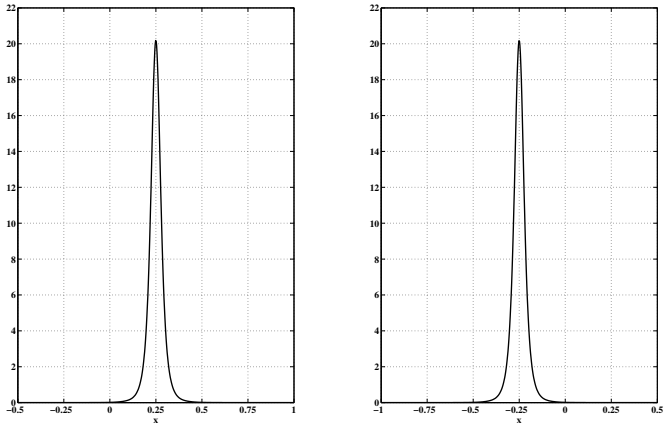

Figure 13.2: Large time behavior of $f(t,s)$ under assumptions (13.5). Simulations are performed with $R=1$, $f^0(s)=\frac{1}{n_1+n_2}$, $n_1=0.5$ and $n_2=1$ (left) or $n_1=1$ and $n_2=0.5$ (right).

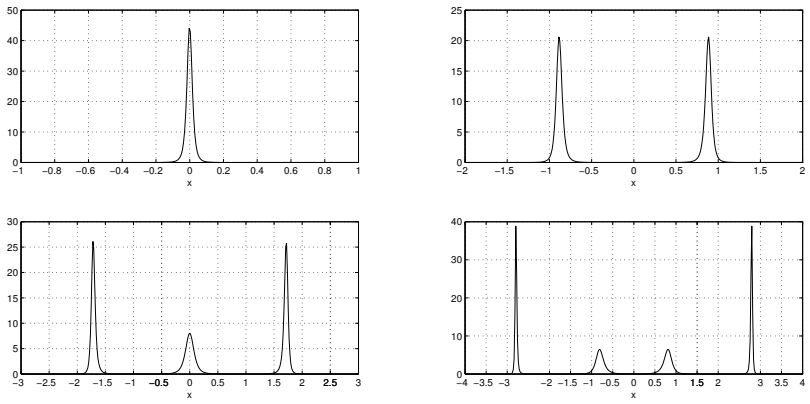

Figure 13.3: Large time behavior of $f(t,s)$ under assumptions (13.7) with $R=1$, for different values of n (i.e. $n=1,2,3,4$).

Chapter 14

A hybrid model for opinion formation [A2]

14.1 Motivations and model

The last fifty years have seen the arising awareness that consistent mathematical models can act as virtual laboratories, providing a framework where those mechanisms that determine the behaviors of large groups of humans can be understood more clearly. Namely, such models may be used to define hypothetical scenarios, whose dynamics can be analyzed with the aim of reducing the gap between the classic Behavioral Theories and the actual behavior of the Modern Society.

When dealing with multiagent systems with a discrete update clock, the model is usually made by a set of finite difference equations describing the evolution of locally interacting agents, whose states are represented by the related opinion with respect to a certain statement. These models are defined on the basis of phenomenological observations and refer to the dynamics of individual opinions.

On the other side, continuous Boltzmann-like kinetic models consist of an evolution equation for a distribution function over the space of microscopic states (i.e. the space of the possible opinions of interacting agents), which characterizes the global state of the system. Such an evolution equation is derived by a balance of the inflow and outflow of agents in the elementary volume of the space of microscopic states and its structure depends on the interactions taken into account.

High flexibility of the related mathematical structures has made the application field of these two classes of models to be extremely wide. However, their applicability domains are significantly different. The former refers to systems composed of a sufficiently small number of agents, while the latter can be effectively applied only in those cases where the number of agents is sufficiently high to be assimilated, at least formally, to a continuum.

This paper is meant to present a mathematical model for opinion formation in a large social group exposed to the persuasive action of strong opinion leaders. The following critical aspects related to the process of opinion formation are included:

1. Humans develop very personal strategies, usually based on mental shortcuts and rules of thumbs. This makes the set of strategies ruling decision-making to be highly heterogeneous.

2. Individuals tend to rely on a relatively small subset of their social group, which is made by those other agents whose opinions are not too much different from their own ones.

3. Most people follow the opinions expressed by those individuals that are recognized as leaders, who form a very small fraction of the whole population and act as the primary source of information for the rest.

4. Interactions among leaders and other individuals, the so-called followers, are highly asymmetric. In fact, strong opinion leaders influence most of the followers, but they are only influenced by other leaders [39]. Moreover, it may happen that a follower is influenced by a strong leader although their opinions are consistently different.

5. Due to the resistance of leaders to change their mind, the dynamics of the leaders' opinions occurs on a longer time scale with respect to the one of the followers.

Point 5 leads us assume the leaders' time scale to be discrete and the one of followers to be continuous. Therefore, also due to point 3, we model the dynamics of the system by coupling a finite difference equation for the dynamics of leaders' opinion and a continuous integro-differential equation of Boltzmann-type for the dynamics of followers. In this sense, the one here proposed is a hybrid model and, within such a formalism, equilibrium is reached when the opinions of leaders and followers condense, across time, into a finite set of distinct and noninteracting opinion clusters. Thus, from a mathematical standpoint, asymptotic analysis are developed with the aim of proving, in the limit of large times, the convergence, in a suitable sense, to highly concentrated solutions.

The reference system is defined by a large social group divided into two interacting subpopulations: one made by a few opinion leaders and the other one composed of a large number of opinion followers. These subpopulations are labeled, respectively, by indexes $i = 1$ and $i = 2$.

The followers change their opinion, along time, as a consequence of interactions among themselves as well as because of interactions with the leaders. On the other hand, due to the strong opinion leader hypothesis, the leaders are assumed to be insensitive to the followers' opinions and to update their own ones through interactions among themselves only. Interactions are supposed to be binary and synchronous, and to involve only agents whose opinions are sufficiently close (i.e. confidence is assumed to be bounded). When one agent

interacts with another one belonging to the same subpopulation, he/she updates his/her opinion to make it closer to the one of the other.

Because of the tendency of leaders to retain their original opinions, we make a temporal scale separation hypothesis, i.e. we assume that the dynamics of leaders occurs on a longer time scale with respect to the one of followers. Thus, the time scale of leaders is modeled by a discrete variable $n \in \mathbb{N}$, while the one of followers is described by a continuous variable $t \in \mathbb{R}^+$.

As previously noted, mathematical models based on a kinetic formalism rely, as such, on the hypothesis that the system is composed of a number of agents sufficiently high, so that its state can be characterized by means of a continuous distribution function. In the present case, this assumption effectively applies to subpopulation 2. As a result, the microscopic state of each follower is identified by a continuous variable $s \in S \subset \mathbb{R}$, which models the opinion expressed with respect to a certain statement. This can be contrary ($s < 0$), neutral ($s = 0$) or favorable ($s > 0$) and the agents support their opinions with a strength described by the absolute value of s. The domain S is assumed to be a symmetric compact set, say $S := [-\sigma, \sigma]$, $\sigma \in \mathbb{R}^+$. The state of subpopulation 2 is identified, at time $t \in \mathbb{R}^+$, by function

$$f : [0, T] \times S \to \mathbb{R}^+, \qquad \int_S f(t, s)ds = 1, \quad \forall\, t \in \mathbb{R}^+,$$

Provided that $s^p f(t, s) \in L^1(S)$, macroscopic quantities can be computed as p-order moments of f at time t. For instance, the total mass (i.e. $p = 0$) and the mean opinion (i.e. $p = 1$) are defined as follows:

$$\rho(t) = \int_S f(t, s)ds = 1, \quad \bar{s}(t) = \int_S sf(t, s)ds.$$

With reference to opinion leaders, we take advantage of the previously drawn considerations and assume subpopulation 1 to be composed of N agents, with N negligible small with respect to the followers' number. At each discrete time instant $n \in \mathbb{N}$, the state of each agent is represented by his/her opinion, which is modeled by a real number $X_j(n) \in S, j = 1, \ldots, N$.

The model here proposed is defined by coupling a finite difference equation, for the dynamics of leaders' opinions, with a time-continuous integro-differential equation of Boltzmann-type, which models the evolution of the function f characterizing the state of followers. Therefore, the dynamics of the system is described by the following Cauchy Problem, which can be derived by providing the model with suitable initial conditions:

$$\begin{cases} X_j(n+1) = X_j(n) + \Xi_j\left[\boldsymbol{X}(n)\right] \\ \\ X_j(0) \in S, \quad j = 1, \ldots, N \\ \\ \partial_t f(t, s) = \mathcal{Q}[f, f](t, s) + \mathcal{K}(t, s) \\ \\ f^0(s) \in L^1(S), \qquad f^0(s) = \frac{1}{2\sigma}, \qquad \int_S f^0(s)ds = 1. \end{cases} \tag{14.1}$$

In the above equations, $\mathbf{X}(n) = (X_1(n), \dots, X_N(n))$ is the vector of the leaders' opinions at time n and $f^0(s)$ is chosen to mimic a scenario where opinion is uniformly distributed among followers at the beginning of observations, so that the average opinion is neutral (i.e. $\bar{s}(0) = 0$), and

$$\begin{aligned}
\Xi_j[\boldsymbol{X}(n)] &= \frac{\tau}{N} \sum_{k=1}^{N} \xi\left(X_k(n) - X_j(n)\right)\left(X_k(n) - X_j(n)\right), \quad j = 0, \dots, N, \\
\mathcal{Q}[f,f](t,s) &= \int_S \int_S \eta^F(s_*, s^*; R^F) Q^F(s|s_*, s^*) f(t, s_*) f(t, s^*) ds_* ds^* \\
&\quad - f(t,s) \int_S \eta^F(s, s^*) f(t, s^*), \\
\mathcal{K}(t,s) &= \sum_{j=1}^{N} \int_S \eta^L(s_*, X_j; R^L) K^L(s|s_*, X_j) f(t, s_*) ds_* - \sum_{j=1}^{N} \eta^L(s, X_j) f(t, s),
\end{aligned} \tag{14.2}$$

with:

$$\tau \in \mathbb{R}^+, \qquad \xi : \mathbb{R} \to \mathbb{R}, \qquad \xi(\cdot) \geq 0, \qquad supp(\xi) := [-R, R], \tag{14.3}$$

$$\eta^F(s_*, s^*; R^F) := \mathbf{1}_{|s_* - s^*| < R_F}, \qquad \eta^F(s_*, s^*; R^F) = \eta^F(s^*, s_*; R^F), \tag{14.4}$$

where $\mathbf{1}$ is the indicator function,

$$Q^F(s|s_*, s^*) := \delta(s - s_F), \qquad S \ni s_F = s_* + \alpha(s^* - s_*), \qquad \alpha \in (0,1), \tag{14.5}$$

where δ is the Dirac's delta distribution,

$$\eta^L(s_*, X_j; R^L) := \chi_{|s_* - X_j| < R_L}, \qquad \eta^L(s_*, X_j; R^L) = \eta^L(X_j, s_*; R^L). \tag{14.6}$$

$$K^L(s|s_*, X_j) = \delta(s - s_L), \qquad S \ni s_L = s_* + \frac{\beta}{N}(X_j - s_*), \qquad \beta \in (0,1). \tag{14.7}$$

14.2 Main results

The existence of a unique non-negative solution for the Cauchy Problem (14.1) is a classical matter, as it can be easily proved by means of standard fixed point arguments.

If $f(t,s)$ solves the Cauchy Problem (14.1), then function $f(nt, s) = f(t_n, s) = f_n(t,s)$ solves the following rescaled problem,

$$\begin{cases}
X_j(n+1) = X_j(n) + \Xi_j\left[\boldsymbol{X}(n)\right] \\
X_j(0) \in S, j = 1, \dots, N \\
\partial_t f_n(t,s) = n\mathcal{Q}[f_n, f_n](t,s) + n\mathcal{K}(t,s) \\
f^0(s) \in L^1(S), \qquad f^0(s) = \frac{1}{2\sigma}, \qquad \int_S f^0(s) ds = 1,
\end{cases} \tag{14.8}$$

The asymptotic dynamics of $\boldsymbol{X}(n)$ and $f(t,s)$ in the limit of large times can be characterized, in an equivalent way, by studying the behavior of $\boldsymbol{X}$ and $f_n(t,s)$ for $n \to \infty$, as established by the following

Theorem 14.2.1 *Assume conditions* (14.4)-(14.7) *to hold. Then, there exists a subsequence of f_n, denoted again as f_n, such that:*

*i) (*Establishing convergence*)*

$$f_n \to f^\infty, \text{ in the weak sense of measure, as } n \to \infty,$$

where f^∞ is a bounded non-negative measure.

*ii) (*Identifying the limit f^∞*)*

Case 1 (Consensus under weak follower-leader interactions).
If $R^F = \sigma$ and $\beta \to 0$, then:

$$f^\infty(s) = \delta(s-0). \tag{14.9}$$

Case 2 (Separation under weak follower-leader interactions).
If $R^F = \frac{\sigma}{2}$ and $\beta \to 0$, then:

$$f^\infty(s) = \frac{\delta(s-s_1)}{2} + \frac{\delta(s-s_2)}{2}, \quad s_1 \in \mathfrak{B}(-\sigma/2, R^F/2),\ s_2 \in \mathfrak{B}(\sigma/2, R^F/2), \tag{14.10}$$

where $s_1 = -s_2$ and $\mathfrak{B}(a,b)$ is the ball of center a and radius b.

Case 3 (Consensus under weak follower-follower interactions).
If $R^L = 2\sigma$, $\alpha \to 0$ and

$$\lim_{n\to\infty} \boldsymbol{X}(n) = \bar{X}1, \quad \bar{X} = \bar{X}(\boldsymbol{X}(0)) \in S,$$

where 1 denotes the constant vector whose components are all one, then:

$$f^\infty(s) = \delta(s-\bar{X}). \tag{14.11}$$

Asymptotic results are illustrated by means of numerical simulations performed in MATLAB making use of a collocation method. With reference to the s variable, a uniform discretization of S consisting of 600 points is selected as computational domain, while the set $[0,T]$ is the reference time domain, where T varies case by case and it is defined as an integer multiple of the time unit $dt = 0.05$.

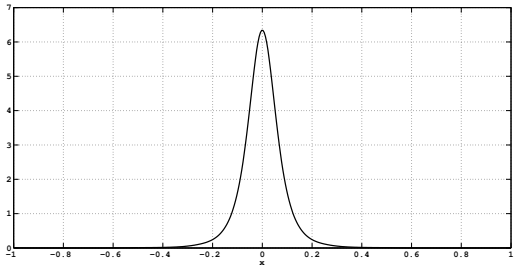

Figure 14.1: Large time behavior of $f(t, s)$ in *Case 1* considered by Theorem 14.2.1. Function f concentrates, across time, around point 0, independently from the influence of leaders. Within the framework of our model, this result provides a mathematical formalization for the emergence of neutral consensus among followers.

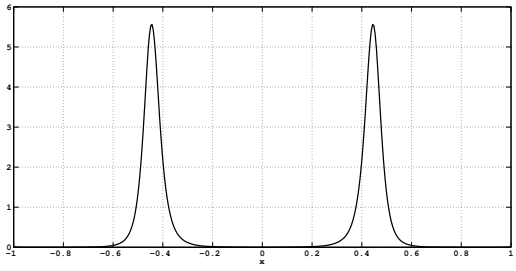

Figure 14.2: Large time behavior of $f(t, s)$ in *Case 2* considered by Theorem 14.2.1. Function f concentrates, across time, around two points that are symmetric with respect to zero and independent from the leader's dynamics. This result provides a mathematical formalization for the idea that, if individuals rely only on a subset of their social group and are weakly influenced by opinion leaders, different parties supporting opposite opinions can emerge.

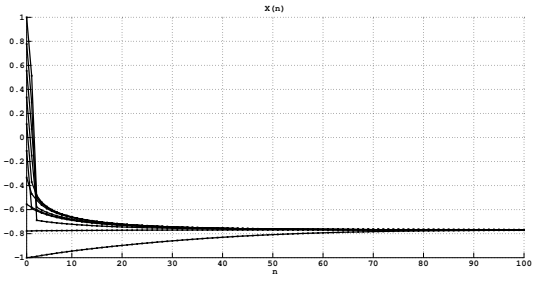

Figure 14.3: Dynamics of $\mathbf{X}(n)$ in *Case 3* considered by Theorem 14.2.1. All components of $\mathbf{X}$ concentrate, across time, around a point $\bar{X}$. This provides a mathematical formalization for the emergence of consensus among leaders.

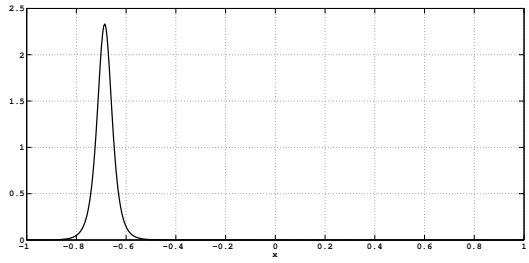

Figure 14.4: Large time behavior of $f(t,s)$ in *Case 3* considered by Theorem 14.2.1. Function f concentrates, across time, around the point $\bar{X}$. This provides a mathematical formalization for the idea that an extremist consensus can be reached in presence of extremist leaders.

Chapter 15

A mathematical model for value estimation with public information and herding [A15]

15.1 Motivations and model

Local and international markets can be seen as complex systems composed of large numbers of interacting agents that try to estimate the value of traded goods on the basis of public and private information as well as of personal feelings.

Agents can be very different from each other and can use the same information in several different ways; thus, the set of all possible estimation strategies is highly heterogeneous.

In principle, if all agents would be fully rational, the value of goods estimated by the market would faithfully reflect all known information about the traded products. Loosely speaking, this is the basic feature that makes a market to be efficient. However, rationality of agents is bounded [65]. This implies that the available information is often not incorporated into those values that emerge from interactions among agents [11].

As a result, the complexity of market dynamics is highly increased by the non rationality that often pervades human behaviors, which can lead individuals to emulate others (herding) or even to do what everyone else is doing regardless what their sources of information suggest to do (naïve herding) [28, 44]. Herding mechanisms can be particularly dangerous in those markets where agents are highly confident in the product. In fact, they can reinforce positive feelings leading the estimated value to grow over-exponentially fast in time; this can be a prelude for the formation of economic bubbles.

The reference system is here defined by a large market, where agents are called to estimate the value of a given product under the influence of some sources of public information, which can affect the evaluation process by suggesting a value for the product under consideration. The market and the information sources are seen as two subpopulations structured, respectively, by $s \in S := [0,1] \subset \mathbb{R}^+$ and $w \in S$. Variable s stands for the value that an agent assigns to the product normalized with respect to a suitable reference value, while variable w models a suitable normalization of the value that information sources suggest to the market. The state of the market at time t is characterized by the function $f(t,s)$

$$f : \mathbb{R}^+ \times S \to \mathbb{R}^+,$$

so that the number density of agents at time t can be computed as

$$\varrho(t) = \int_S f(t,s)ds$$

and the value estimated by the market is modeled by the function

$$\bar{s}(t) = \frac{\int_S sf(t,s)ds}{\varrho(t)}. \tag{15.1}$$

On the other hand, the state of the information sources is identified by function $g(t,w)$

$$g : \mathbb{R}^+ \times S \to \mathbb{R}^+,$$

which is supposed to be a given non-negative function of its argument such that

$$g(t,s) \in C(\mathbb{R}^+; L^1(S)), \quad \int_S g(t,s)ds = 1. \tag{15.2}$$

The estimated value $\bar{s}(t)$ results from a dynamical equilibrium and it can be computed if $f(t,s)$ is known. Function f evolves according to the following initial value problem

$$\begin{cases} \partial_t f(t,s) = \mathcal{Q}^I[f,g](t,s) + \mathcal{Q}^H[f,f](t,s) \quad s \in S, \quad t > 0 \\ f(0,s) = f^0(s) \in L^1(S), \quad f^0(s) \geq 0 \ a.e.\ on\ S, \quad \int_S f^0(s)ds = 1, \end{cases} \tag{15.3}$$

where:

$$\begin{aligned} Q^I[f,g](t,s) &:= \int_S \int_S \eta^I(s_*,s^*;R^I)Q^I(s|s_*,s^*;\alpha)f(t,s_*)g(t,s^*)ds_*ds^* + \\ &- f(t,s)\int_S \eta^I(s,s^*)g(t,s^*)ds^*, \\ Q^H[f,f](t,s) &:= \int_S \int_S \eta^H(s_*,s^*;R^H)Q^H(s|s_*,s^*;\beta)f(t,s_*)f(t,s^*)ds_*ds^* + \\ &- f(t,s)\int_S \eta^H(s,s^*)f(t,s^*)ds^*. \end{aligned} \tag{15.4}$$

With reference to Eqs. (15.4):

$$Q^I(s|s_*, s^*; \alpha) := \delta\left(s - (s_* + \alpha(s^* - s_*))\right), \qquad \alpha \in (0,1) \subset \mathbb{R}^+, \tag{15.5}$$

where δ is the Dirac's delta distribution. The above definition relies on the idea that if agents in the market trust an information source, then they update their value to make it closer the one suggested by the source.

$$\eta^I : S \times S \to \{0,1\}, \quad \eta^I(s_*, s^*; R^I) := \mathbf{1}_{\{|s_* - s^*| \leq R^I\}}, \quad R^I \in (0,1], \tag{15.6}$$

where $\mathbf{1}$ is the indicator function,

$$Q^H(s|s_*, s^*; \beta) := \delta\left(s - (s_* + \beta(s^* - s_*))\right), \qquad \beta \in (0,1) \subset \mathbb{R}^+ \tag{15.7}$$

and

$$\eta^H : S \times S \to \{0,1\}, \quad \eta^H(s_*, s^*; R^H) := \mathbf{1}_{\{|s_* - s^*| \leq R^H\}}, \quad R^H \in (0,1], \tag{15.8}$$

or

$$\eta^H : S \times S \to \mathbb{R}^+, \quad \eta^H(s_*, s^*; R^H) := \xi(s_*, s^*; R^H), \tag{15.9}$$

where function ξ is defined as

$$\xi(s_*, s^*) := \begin{cases} \dfrac{s^*(1 - s_*)}{R^H(s^* - s_*)}, & \text{if } s^* > s_* \\ 0, & \text{otherwise.} \end{cases} \tag{15.10}$$

Definitions (15.6) and (15.8) rely on the idea that interactions occur, at time t, only among agents and informations sources, or among agents themselves, whose estimated values are at a distance smaller than a threshold value R^I, or R^H. On the other hand, definition (15.9) mimics a socio-economic scenario where agents are highly confident in the product.

15.2 Main results

The existence of a unique non-negative solution for the Cauchy Problem (15.3) is a classical matter, as it can be easily proved by means of standard fixed point arguments.

The asymptotic behavior of $f(t, s)$ in the limit $t \to \infty$ is characterized by the following theorem, whose proof relies on standard techniques of functional analysis together with direct computations involving the time derivative of function f under different parameter settings:

Theorem 15.2.1 *There exists a subsequence of f, denoted again as f, such that:*

*i) (*Establishing convergence*)*

$$f \to f^{\infty}, \text{ in the weak sense of measure, as } t \to \infty,$$

where f^{∞} is a bounded non-negative measure.

*ii) (*Identifying the limit f^{∞}*)*

Case 1 (efficient market).
If $R^I = 1$, $g(t,s) = g(s) = \delta(s - \hat{s})$ with $\hat{s} \in S$ for any $t \geq 0$ and $\beta \to 0$, then:

$$f^{\infty}(s) = \delta(s - \hat{s}). \tag{15.11}$$

Case 2 (naïve herding).
If η^H is defined by (15.8) with $R^H \geq \max(\bar{s}(0), 1 - \bar{s}(0))$ and $\alpha \to 0$, then:

$$f^{\infty}(s) = \delta(s - \bar{s}(0)). \tag{15.12}$$

Case 3 (bubble formation).
If η^H is defined by (15.9) and $\alpha \to 0$, then

$$f^{\infty}(s) = \delta(s-1) \quad \textit{and} \quad \frac{d}{dt}\bar{s}(t) \geq C\bar{s}(t)(1 - \bar{s}(t)), \quad C \in \mathbb{R}^{+}. \tag{15.13}$$

Asymptotic results are illustrated by means of numerical simulations performed in MATLAB making use of a collocation method. With reference to the s variable, a uniform discretization of S consisting of 600 points is selected as computational domain, while the set $[0, T]$ is the reference time domain, where $T = 10$ is an integer multiple of the time unit $dt = 0.05$. Throughout simulations we assume $g(t,w) = g(w) \approx \delta(w - 0.63)$ for all $t \in [0, T]$.

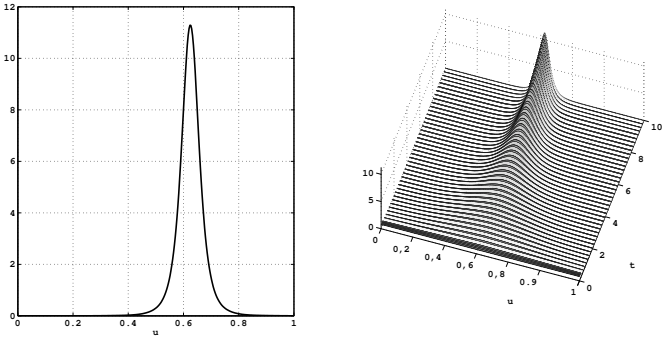

Figure 15.1: Large time behavior (left) and evolution in time (right) of $f(t,s)$ in *Case 1* considered by Theorem 15.2.1. Function f concentrates, across time, around the point $\hat{s} = 0.63$ where g is highly concentrated. Thus, all the agents concentrate, in the limit of large times, around the same value, which is the one suggested by information sources. Within the framework of our model, this result provides a mathematical formalization for the efficient market transition.

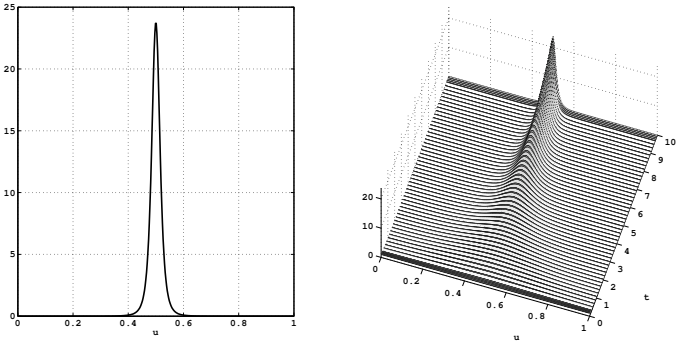

Figure 15.2: Large time behavior (left) and evolution in time (right) of $f(t,s)$ in *Case 2* considered by Theorem 15.2.1. Function f concentrates, across time, around the point $\bar{s}(0) = 0.5$, which is independent from g. Thus, in the limit of large times, all the agents estimate the same value, which is equal to the one defined by the market as a whole at the beginning of observations and is independent from public information. This result provides a mathematical formalization for the idea that the market efficiency hypothesis does not apply in those cases where naïve herding occurs.

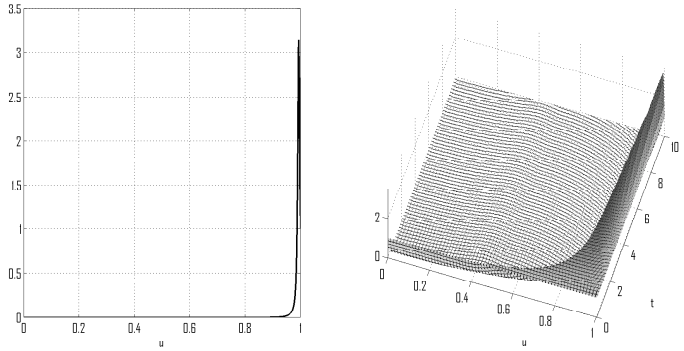

Figure 15.3: Large time behavior (left) and evolution in time (right) of $f(t, s)$ in *Case 3* considered by Theorem 15.2.1. Function f concentrates, across time, around the point 1. Thus, as time goes by, all the agents tend to estimate the same high value for the product. This result provides a mathematical formalization for the idea that naïve herding can lead agents to estimate a very high value for traded products in a weakly rational and highly confident market.

Part VI

Conclusions and Research Perspectives

Mathematical models can act as *virtual laboratories*, providing a framework where mechanisms that determine the behaviors of *large groups of living beings* can be understood more clearly. Even more, these models can be used to define some *hypothetical scenarios*, whose dynamics can be analyzed to reveal new insights into behaviors that have not yet been observed, thus reducing the gap between theory and experimental observations.

Moving from these observations, after a brief overview on the distinguishing features of complex living systems, we have presented a possible strategy to reduce complexity in view of the mathematical modeling. This strategy combines the formal structures pertaining to *mathematical models for unstructured and structured populations*. In particular, the focus has been on phenotype-structured equations, space-velocity-structured equations (i.e. kinetic-like equations) and opinion-structured equations.

An overview over the models that we have so far defined making use of such a strategy has been provided. The related reference systems belong to three wide classes of complex living systems, that is, *living species, multicellular systems and socio-economic systems*. Most of the models for multicellular systems stem from *direct collaborations with biologists and clinicians*.

From an applicative perspective, we have highlighted the ability of these models to *mimic emergent behaviors and self-organizing abilities* expressed by the complex living systems under consideration. However, additional efforts are needed to make the outputs of the present models more consistent with physical reality. For instance, *ad hoc* experiments should be designed to assign precise values to the model parameters. This could also be a first step to make the present models useful not only to reproduce qualitative behaviors but also to produce quantitative forecasts.

On the other hand, from a mathematical standpoint, besides *local and global existence results* for the mathematical problems linked to the models, we have developed *asymptotic analysis* meant, on the one side, to *derive macroscopic equations* that can be interpreted more directly than the underlying mesoscopic models and, on the other side, to prove the *weak convergence of the solutions to sums of Dirac masses* over the space of structuring variables. This kind of weak convergence results provides a possible mathematical formalization both for the selection principle of evolutionary biology and the emergence of opinions. Finally, we have performed numerical simulations with the aim of illustrating and extending analytical results.

Future research activities will aim at *extending and modifying the proposed models* in order to enlarge their application domains. Such extensions and modifications will require additional efforts from the modeling, the analytical and the numerical point of views, as implied by the research lines below summarized. Let us notice that investigations on these topics will be developed in the framework of already established *international collaborations*, involving also other scientists in addition to some of those who took part in the research here presented.

Living species

- *Sexual reproduction.* The models presented in Part III assume that proliferation does not require any kind of interactions among individuals belonging to the reference system. This implies that these models effectively apply only to living species proliferating through asexual reproduction and causes a strong limitation in the model application domains. As a result, it would be useful to extend the equations here presented in order to include the effects of sexual reproduction. In turn, this would requires the design of new analytical approaches to develop the same kind of asymptotic analysis here proposed, with the aim of mimicking the emergence of speciation and the formation of evolutionary branching patterns.

- *Spatially heterogeneous environment.* All of the models for living species here considered implicitly rely on the assumption that individuals share the same environment, independently from their space positions. However, in several practical cases, living species are embedded into spatially heterogeneous domains and their evolutionary dynamics can be strongly affected by local conditions. In this respect, it would be interesting to extend the considered phenotype-structured equations to model, for instance, the evolution of living populations also structured in space [4]. This may require developing suitable analytical strategies that can handle, at the same time, integro-differential formalism used to describe evolutionary dynamics as well as differential formalism modeling space dynamics.

Multicellular systems

- *Dimorphism and polymorphism.* The phenotype-structured equations for the evolutionary dynamics of healthy and cancer cells proposed in Chapter 12 need to be modified in order to describe the dynamics of multicellular systems structured by higher dimensional variables, where multiple traits can be selected at the same time (i.e. dimorphism and polymorphism can arise), so that the emergence of intra-tumour heterogeneity can be effectively reproduced. In particular, the case of cell populations structured also in space should be considered, where the dynamics of diffusing nutrients and therapeutic agents are explicitly included.

- *Resistance to anti-cancer therapies and therapy optimization.* Taking again advantage of the models presented by Chapter 12, it would be interesting to consider phenotype-structured equations for the evolutionary dynamics of cancer cells under the effects of adaptive therapies [33], metronomic chemotherapy [2] and infusion protocols based on bang-bang control [10]. The underlying idea is to inspect the effects of these therapeutic strategies looking for the design optimized anti-cancer treatments.

  Starting from the specific model for hepatocellular carcinoma presented in Chapter 7, a more general model for the dynamics of cancer cells under the effects of targeted therapeutic agents could be designed, in order to

deepen further the role that this kind of drugs plays in the development of tumors. In this sense, the identification of a suitable asymptotic method allowing to pass from integro-differential equations describing the dynamics of the reference multicellular system at the mesoscopic scale to ordinary differential equations for the macroscopic evolution could be useful. On the one side, this would make it possible to analyze how mechanisms at the cell level generate global phenomena at the whole tumor level. On the other side, it would allow to take advantage of well established techniques for optimal control problems in the ODEs context [10], which can provide a better understanding of cancer response to therapies.

- *Space organization of phenotypic traits.* Structured equations modeling the progressive growth of solid tumor aggregates should be considered. In particular, in perspective to the results presented in [13], where a simple reaction–diffusion equation has been used to study qualitative properties of invasion fronts arising in ecology, equations presented in Chapter 8 and Chapter 9 should be suitably modified in order to study the formation of invasion fronts in cancer, where motility can vary from one cell to another according to phenotypic criteria.

Socio-economic systems

- *Intricate followers-leaders interactions.* With reference to asymptotic results presented in Chapter 14, future works could be addressed to study how the dynamics of the followers is affected by the leaders' opinion in those cases where the leaders reach consensus and the followers trust the leaders if and only if their opinions are sufficiently close.

- *Interactions over small networks.* Social networks play nowadays a prominent role in shaping public opinion. In this sense, focusing on networks composed of small numbers of nodes, it would be interesting to identify suitable modeling strategies to take into account the influence of the network topology on the interactions among individuals. In particular, along the lines of the model presented in Chapter 14, continuous structured equations could be used to describe the opinion dynamics within each node, while interactions among nodes could be characterized through an agent-based formalism.

- *Learning and memory aspects.* The models here presented could be suitably extended to account for the fact that individuals tend to learn from their past experiences, so that the opinions expressed at the present time also depend on the individuals' memories of the past. This could lead to define delayed integro-differential equations, whose qualitative analysis should require the identification of new analytical approaches compared to the ones that we have so far developed.

Personal Contributions

Papers published in refereed journals

A1 D. Borra, T. Lorenzi, Asymptotic analysis of continuous opinion dynamics models under bounded confidence, *Commun. Pure Appl. Anal.*, 12 (2013) 1487–1499.

A2 D. Borra, T. Lorenzi, A hybrid model for opinion formation, *Z. angew. Math. Phys.*, DOI: 10.1007/s00033-012-0259-z, 2012.

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Appendix